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Inclusion, characteristics and outcomes of people requiring palliative care in studies of non-pharmacological interventions for delirium: a systematic review

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Keywords:	clinical trial, delirium, hospice, inpatient, palliative care, review
Abstract:	Background Delirium is common, distressing, serious and under-researched in specialist palliative care settings. Objectives To examine whether people requiring palliative care were included in non-pharmacological delirium intervention studies in inpatient settings, how they were characterised, and what their outcomes were. Design Systematic review (PROSPERO 2017 CRD42017062178). Data sources

	Systematic search in March 2017 for non-pharmacological delirium intervention studies in adult inpatients. Database search terms were 'delirium', 'hospitalisation', 'inpatient', 'palliative care', 'hospice', 'critical care', 'geriatrics'. Scottish Intercollegiate Guidelines Network methodological checklists guided risk of bias assessment. Results The 29 included studies were conducted between 1994-2015 in diverse settings in 15 countries (9136 participants, mean age 76.5 years [SD 8.1], 56% women). Most studies tested multicomponent interventions (n=26) to prevent delirium (n=19). Three-quarters of the 29 included studies (n=22) excluded various groups of people requiring palliative care; however, inclusion criteria, participant diagnoses, illness severity and mortality indicated their presence in almost all studies (n=26). Of these, 21 studies did not characterise participants requiring palliative care or report their specific outcomes (72%), four reported outcomes for older people with frailty, dementia, cancer and comorbidities, and one was explicitly focused on people receiving palliative care. Study heterogeneity and limitations precluded definitive determination of intervention effectiveness and only allowed interpretations of feasibility for people requiring palliative care. Acceptability outcomes (intervention adverse events and patients' subjective experience) were rarely reported overall. Conclusion Non-pharmacological delirium interventions have frequently excluded and under-characterised people requiring palliative care and infrequently reported their outcomes.

Inclusion, characteristics and outcomes of people requiring palliative care in studies of non-pharmacological interventions for delirium: a systematic review

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Abstract

Background

Delirium is common, distressing, serious and under-researched in specialist palliative care settings.

Objectives

To examine whether people requiring palliative care were included in non-pharmacological delirium intervention studies in inpatient settings, how they were characterised, and what their outcomes were.

Design

Systematic review (PROSPERO 2017 CRD42017062178).

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Systematic search in March 2017 for non-pharmacological delirium intervention studies in adult inpatients. Database search terms were 'delirium', 'hospitalisation', 'inpatient', 'palliative care', 'hospice', 'critical care', 'geriatrics'. Scottish Intercollegiate Guidelines Network methodological checklists guided risk of bias assessment.

Results

The 29 included studies were conducted between 1994-2015 in diverse settings in 15 countries (9136 participants, mean age 76.5 years [SD 8.1], 56% women). Most studies tested multicomponent interventions (n=26) to prevent delirium (n=19). Three-quarters of the 29 included studies (n=22) excluded various groups of people requiring palliative care; however, inclusion criteria, participant diagnoses, illness severity and mortality indicated their presence in almost all studies (n=26). Of these, 21 studies did not characterise

participants requiring palliative care or report their specific outcomes (72%), four reported outcomes for older people with frailty, dementia, cancer and comorbidities, and one was explicitly focused on people receiving palliative care. Study heterogeneity and limitations precluded definitive determination of intervention effectiveness and only allowed interpretations of feasibility for people requiring palliative care. Acceptability outcomes (intervention adverse events and patients' subjective experience) were rarely reported overall.

Conclusion

Non-pharmacological delirium interventions have frequently excluded and under-characterised people requiring palliative care and infrequently reported their outcomes.

Key words

Clinical trial, Delirium, Hospice, Inpatient, Palliative Care, Review

Key statements

What is already known about the topic?

- Delirium is a distressing and serious neurocognitive condition that frequently occurs for patients in palliative care inpatient settings.
- In contrast to other hospital settings, there is limited evidence to guide non-pharmacological intervention to prevent and treat delirium in palliative care inpatient settings.

What this paper adds

- This review found that various groups of people requiring palliative care were excluded from three-quarters of non-pharmacological delirium intervention studies in inpatient settings; despite this, they were present in most studies and their outcomes were reported in five.
- Non-pharmacological delirium interventions appear feasible for people requiring palliative care yet there is no definitive evidence they are effective or acceptable for this inpatient group.

Implications for research

- Phase II and III randomised controlled trials of non-pharmacological interventions to prevent and treat delirium are needed in specialist palliative care settings.
- Adaptations to future trials of non-pharmacological delirium interventions in other inpatient settings are needed to promote representative study populations and allow outcomes for sub-groups of people requiring palliative care to be reported.
- Additional outcomes related to patient and family subjective experience, goals of care and quality of life would enhance the relevance of delirium intervention research in inpatient settings where people are cared for at the end of life.

Introduction

Delirium is a serious complication of medical illness and hospitalisation.[1] The condition is characterised by acute disturbances to attention, awareness and cognition, has multifactorial aetiology, and variously affects memory, language and visuospatial ability, orientation and perception.[2] Affected persons often experience feelings of fear, humiliation, confusion and disconnection from others.[3, 4] Family members' experience distress when delirium causes sudden changes in behaviour and decline in the person they love.[5 6] Patients who experience an episode of delirium during hospitalisation experience many poorer outcomes, including being more likely to die.[1, 7, 8]

Delirium most often occurs in people with older age, advanced or severe illness and/or pre-existing cognitive impairment. Hospital-wide, one in five patients have delirium,[9] with occurrence higher again in intensive, geriatric and palliative care units.[1, 6] Studies of delirium epidemiology in palliative care inpatient units that screened patients at least daily reported incidence of 33–45% and prevalence of 58-88% in those who died.

Development of delirium guidelines[1, 10-13] policy[14] and international advocacy[15] indicate growing awareness of the seriousness and prevalence of delirium and importance of evidence based care for hospitalised patients.[16, 17] There now is sufficient evidence to implement non-pharmacological interventions for delirium in certain hospital settings.[18, 19] For example, reviews of studies of multicomponent interventions addressing physical and cognitive activity, sleep, hearing, vision and hydration, as in the original Hospital Elder Life Program (HELP) study,[20] reported reduction in incident delirium in older hospitalised patients.[21-23] Reduction in length of hospital stay and improvement in return to independent living were also demonstrated.[22]

In contrast, guideline recommendations for non-pharmacological interventions as the first approach to prevent and treat delirium during advanced illness and at the end of life are not evidence based.[10, 17, 24] A recent scoping review reported the need to generate evidence to inform clinical care in palliative care settings and populations, for non-pharmacological interventions in particular.[25] Poorer outcomes with antipsychotics,[26] and over-sedation

when benzodiazepines were given for agitated delirium,[27] in two recent trials in specialist palliative care settings also highlight the need to establish 'drug-free' ways to prevent and relieve the difficulties of delirium at the end of life.

In response, the authors established the '*Studies to Understand and Improve Delirium Care in Palliative Settings*' international collaborative (SUNRISE) to generate high-quality delirium research in palliative care. We identified the need to inform our future trials in palliative care through a review of studies of non-pharmacological interventions for delirium conducted in a wide range of inpatient settings. This wide review was premised on our clinical experience and knowledge that many hospitalised patients have advanced and/or serious illness, frailty and high comorbidity and consequently much in common with patients in specialist palliative care settings, especially those in intensive care, medical and geriatric units where rates of delirium are similarly high. [28, 29] Based on this premise, our specific objectives were to examine whether people requiring palliative care were included in non-pharmacological delirium intervention studies in various inpatient settings, how these participants were characterised, and whether the non-pharmacological interventions were effective, feasible and/or acceptable for them.

Methods

Design

Systematic review of the literature, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[30]

Participants/settings

Adults (≥18 years) receiving inpatient hospital or hospice care. In this review, we refer to 'hospice' as an inpatient facility with the primary function to provide specialist palliative care to people with life-threatening illness, and analogous to a palliative care inpatient unit.

Search strategy

In March 2017, we searched MEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library and Web of Science with the following search terms in MEDLINE: Delirium AND Hospitalization

OR Inpatient OR Hospice AND Palliative Care OR Critical Care OR Geriatrics. Filters in Medline were: 1. Study types: clinical study, clinical trial all, comparative study, controlled clinical trial, meta-analysis, multicenter study, pragmatic clinical trial, randomised controlled trial, systematic review; 2. Peer reviewed journal and 3. Published from 1980 onward (when delirium was first included in the American Psychological Association (APA) Diagnostic and Statistical Manual (DSM-III).[31] We tailored search terms and filters to subsequent databases. We examined reference lists of relevant systematic reviews and meta-analyses identified in the search for additional eligible studies.

Inclusion/exclusion criteria

Studies included were primary reports of prospective trials (i.e. studies of an intervention with a comparator); with a primary objective to prevent or treat delirium through non-pharmacological intervention/s in adult patients in hospital or hospice unit settings; a primary outcome of delirium incidence, severity or duration; published in English in a peer-reviewed journal.

Studies excluded were reports of interventions for alcohol withdrawal delirium only; systematic reviews and meta-analyses of non-pharmacological delirium intervention/s; studies where the primary outcome was not participants' delirium status (e.g. process or cost effectiveness outcomes, validation of delirium tools); studies that did not use diagnostic criteria or a tool with established psychometric properties to measure delirium; protocols; and ongoing studies.

Study selection, data extraction and management

We imported search results into Endnote X7 software, removed duplicates and exported results to Covidence,[32] where three reviewers [IAD, LE, AH] independently applied eligibility criteria to titles and abstracts. Reviewers compared decisions about inclusion, documented reasons for exclusions at full text review and resolved discrepancies through discussion. Two reviewers [IAD, LE] extracted data according to the template for intervention description and replication (TIDieR) checklist and guide [33] into an Excel V15.28 spreadsheet. The lead reviewer [AH] contributed guidance, oversight and independent data checking.

Risk of bias assessment

Two reviewers [LE and AH] independently assessed each study for selection, performance, detection, attrition, confounding, and reporting biases according to the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklists[34] for controlled trials and cohort studies. Discrepancies were resolved through discussion.

Outcomes

To identify our sample of interest (i.e. people requiring palliative care), we examined study inclusion and exclusion criteria, participant diagnoses (including severity or staging), and mortality. We assessed eligibility criteria and diagnoses against the Gold Standards Framework Proactive Identification Guidance (GSF PIG), a clinical tool to help identify people likely to need additional supportive (i.e. palliative) care in the last 12 months of life.[29] According to the GSF PIG, these people are those with life-threatening conditions, including illnesses that are advanced, progressive, incurable and/or likely to cause acute crises; frailty and co-morbidities; and sudden catastrophic events.

Previous reviews have reported effectiveness outcomes of non-pharmacological delirium interventions for the entire study sample; [21-23] whereas this review focused on effectiveness, feasibility and acceptability outcomes of our sample of interest. We examined effectiveness according to each study's primary outcome and any sub-group analysis for our sample of interest. We assessed feasibility by examining intervention characteristics, adherence and study modifications, and acceptability through intervention-related adverse effects and patient, family, clinician and volunteer subjective experiences of the interventions.

Synthesis and analysis plan

We generated tables, text and graphs to report study characteristics, participants, interventions and outcomes. Data transformation and descriptive numerical analyses were performed using Excel. We planned to perform subgroup meta-analysis using Review Manager Analyses software [35] of intervention effectiveness if we could definitively distinguish our sample of interest and if interventions and comparators and measures were comparable.

Updated search

We updated the search prior to publication in February 2019 and identified two new eligible papers published after the original search date.[36, 37] There were not incorporated as neither paper altered the conclusions of the review.

Results

The original database search strategy generated 4300 records. After removing 35 duplicates and 4169 records through title and abstract screening, we reviewed 69 full text papers and excluded 48. We included another eight through reference list searching, resulting in 29 papers reporting 29 studies for inclusion (Figure 1).

(Insert Figure 1 PRISMA Flow Diagram here)[30]

Study characteristics

The 29 studies were conducted between 1994-2015 across 15 countries: six in the US,[38 39 40 41 42 20] three each in Australia,[43 44 45] Belgium,[46-48] and Canada,[49-51] two each in the Netherlands[52, 53] and Sweden,[54, 55] and one each in Chile,[56] France,[57] Ireland,[58] Italy,[59] Japan,[60] Korea,[61] Singapore,[62] Spain,[63] UK,[64] and the US/Canada[65] (Table 1).

Study designs were before/after studies (one with an additional concurrent arm[62]) (n=11),[38-41, 44, 45, 48, 52, 57, 62, 64] randomised controlled trials (RCTs) (n=10),[42, 43, 47, 50, 51, 53, 55, 56, 61, 65] non-randomised controlled trials (one with matched participants[20]) (n=5),[20, 46, 54, 59, 63] a quasi-experimental study,[49] a pilot randomised controlled trial,[60] and a comparative time series study.[58]

Services and settings were medical (n=10),[20, 41, 43, 50-52, 54, 56, 59, 63] geriatric (n=7),[39, 44, 55, 57, 59, 62, 63] medical and/or surgical intensive care (n=6),[38, 40, 47, 58, 61, 64] perioperative hip fracture (n=6),[42, 45, 46, 48, 55, 65] other perioperative (n=3) [52, 53, 60] and palliative care and hospice units (n=1), [49] with eight studies involving more than one service.[47, 52, 55, 58, 59, 61, 63, 64]

Most studies tested multicomponent interventions (n=26) and aimed to prevent delirium in non-delirious participants (n=19) (Table1). Six studies aimed to prevent and treat delirium [38, 42, 48, 54, 55, 65] three were treatment only studies.[50, 51, 62]

(Insert Table 1 Study characteristics here)

Code: P Prevention, **T** Treatment, **RCT** Randomised controlled trial, **CTS** Comparative time series, **B/A** Before–after study, **CT** Controlled trial, **ICU** Intensive Care Unit, **NR** Not reported, **MC** Medical Centre, **M** Multicomponent, **PRCT** Pilot RCT, **QE** Quasi-experimental, **S** Single component

$^{\Delta}$ Numbers signify the domains in which the study was assessed as having **low risk of bias**: 1 = Representative study sample; 2 = Concealed allocation; 3 = Random sequence generation; 4 = Blinded participants and intervention personnel; 5 = Blinded outcome assessors; 6 = Valid, reliable delirium measures; 7 = <20% sample lost to analysis; 8 = Intention to treat analysis; 9 = Confounders accounted for; 10 = Only *a priori* outcomes reported

Risk of bias assessment

Almost all studies were assessed as having at least one form of selection bias (n=28). The exception was a Chilean RCT of a prevention intervention where family members delivered cognition, vision, and hearing strategies to patients.[56] Eight RCTs minimised internal selection bias through concealed allocation and random sequence generation.[42, 43, 47, 50, 53, 55, 56, 65] There was high risk of performance bias in all studies, due to the inherent difficulty of blinding non-pharmacological interventions: one RCT blinded participants to their allocation, [43] and no studies blinded those performing the intervention. Detection bias was minimised in eight studies through blinded outcome assessors combined with valid, reliable delirium measures.[42, 43, 47, 50, 51, 53-55] Although we excluded studies that did not use delirium diagnostic criteria and/or a tool with established psychometric properties, three studies were assigned uncertain risk of detection bias due to retrospective assignment of delirium status when the Confusion Assessment Method (CAM) was not performed during weekends in two before-after studies;[41, 45] and when delirium incidence was reported as a mean rather than a proportion in a comparative time series study.[58] High risk of detection bias was assigned to a delirium prevention study in seven Canadian palliative care units due use of a screening tool, the Confusion Rating Scale (CRS) to measure delirium incidence, severity and duration.[49] Six studies had low risk of attrition bias.[42, 43, 50, 55, 56, 63] Confounders were accounted for in 17 studies.[20, 39, 40, 42, 46, 47, 49-52, 54, 55, 58, 59, 61, 63, 65] Most studies (n=22) reported only *a priori* outcomes,[20, 38-43, 46, 48, 50-53, 55-57, 60-65] which we assessed by information provided within the papers rather than through examination of trial registrations or published protocols, which no studies cited.

Figure 2 presents overall risk of bias in the included studies.

(Insert Figure 2 Overall risk of bias graph here)

Figure 2: Overall risk of bias

Participant characteristics

There were 9136 participants (n=4553 in intervention arms) across the 29 studies (Table 2). Sample sizes ranged from 15-1516 participants. Participants' overall mean age (excluding two studies that reported only age range or median) [48, 58] was 76.5 years (SD ± 8.1). There were more female participants (56%) than male.

Inclusion and exclusion criteria

Inclusion

Most studies (n=19) included only patients aged 65 years and older (Table 2). Twenty-two studies included consecutively admitted patients, 16 of which further required certain physical conditions to be present (e.g. frailty,[53] hip fracture,[42, 45, 46, 48, 55, 65] anemia,[65] dementia,[57] advanced cancer,[49] oesophageal cancer surgery[60]). Five studies included only patients with risk factors for delirium[20, 44, 52, 56, 63] and three included only patients with delirium.[50, 51, 62] The study in seven Canadian palliative care units (hereafter termed the 'palliative care unit study') included only patients with terminal cancer, defined as dying within 90 days of admission which was retrospectively identified. This study had the largest sample of all the studies (n=1516, 17%).[49]

Exclusion

Twenty-three studies excluded patients on various diagnostic grounds (Table 2). These were stroke or cerebrovascular accident (CVA), moderate-severe traumatic brain injury or coma (n=9);[20, 38, 43, 48, 50, 51, 59, 62, 63] dementia or prior cognitive impairment (n=7);[20, 38, 44, 47, 61, 63, 64] psychiatric disorders or alcohol/drug addiction (n=6);[43, 44, 59-61, 64] pathological fracture (n=4);[46, 48, 55, 65] poly- or multiple trauma (n=2);[46, 48] neurologic diagnosis/neurosurgical (n=2);[61, 64] metastatic cancer or referred to oncology services (n=2);[42, 50] and others (myocardial infarction,[65] severe renal failure,[55] brain concussion,[48] history of sleep pathology,[64] severe rheumatoid arthritis [55] and severe hip osteoarthritis[55]).

Fifteen studies excluded patients with impaired verbal communication or who were otherwise unable to complete study assessments.[20, 38, 39, 41, 43, 46, 48, 50, 52, 53, 59, 61-63, 65] Six studies excluded patients with hearing and/or visual impairment.[46-48, 60, 61, 64] Three studies excluded patients isolated for infection.[43, 61, 62]

Eight studies explicitly excluded patients expected to die, using the following terms: "terminal diagnosis" or "terminal illness" (n=3),[20, 58, 62] "terminal condition and receiving comfort care" (on the basis that they were unlikely to benefit from the intervention) (n=2),[41, 44] "life expectancy less than six months",[46] "metastatic cancer or comorbid illnesses likely to reduce life expectancy to less than six months",[42] "death expected within 24 hours",[43] and "dangerously ill".[62]

Two studies excluded participants who subsequently died from analysis;[51, 52] a delirium prevention study in elderly care wards excluded 70% of 2162 admitted patients due to being "too unwell"; [39] and another study excluded patients with "deterioration of condition".[60]

The palliative care unit study excluded patients who lived for more than 90 days or who were still alive at discharge from analysis.[49]

Characterisation of study participants

Participant diagnoses and illness severity

Reporting of participant diagnoses, illness severity and mortality varied. Fifteen studies reported co-morbid diagnoses, twelve reported only primary diagnoses, and four reported both (Table 2). Diagnoses' categorisation varied. Studies rarely reported staging of diagnoses (n=2).[49, 56]

Sixteen studies reported illness severity for all participants using at least one measure, more often as a mean or median score (n=15)[20, 38, 43, 46, 47, 50, 52, 55, 56, 59, 61-65] than by categorising participants proportionally (n=6).[20, 39, 42, 47, 52, 62] The most frequently used illness severity measures were the Charlson Comorbidity Index (CCI)[66] (n=7; reported as: mean scores 2.3 - 3.3,[46, 50, 62] median 2,[43, 56] and scores of four or greater 19.8%[39] and 39%[42]); and the Acute Physiology And Chronic Health Evaluation II (APACHE II) [67] (n=6; mean scores 11.3-15.6).[20, 43, 59, 61, 63, 64] Two ICU studies that measured illness severity using the APACHE II reported

means scores (13.9-14.6) [61, 64] approximately equivalent to or less than those reported in three of four medical and geriatric unit studies (14.1-15.6).[20, 43, 59] Other measures were the Cumulative Illness Rating Scale–Geriatrics (CIRS-G) comorbidity and severity indexes;[52, 59, 68] American Society of Anesthesiologists physical status classification (ASA)[52, 65, 69]; Blessed Dementia Rating Scale;[20, 42, 70] Modified Early Warning Score (MEWS);[39, 71] Sepsis-related Organ Failure (SOFA);[47, 72] Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE);[47, 73] Simplified Acute Physiology Score (SAPS 3);[47, 74] and the 15-item Geriatric Depression Scale (GDS-15).[55, 75]

Three studies reporting comorbidities without the CCI reported: i. 60% had more than two comorbidities (diabetes, COPD, hypertension, myocardial infarction, other cardiovascular disorders, neurological disorders, cerebrovascular disorders, hearing and vision problems, memory problems in daily life, psychiatric disorders or musculoskeletal disorders);[53] ii. 72% had at least one co-morbid illness;[47] and iii. a mean of 2.7 comorbidities.[63]

Almost every diagnosis, sensory deficit and impairment that were exclusion criteria in some studies were reported in the overall study population (Table 2). For example, more studies reported participants with dementia or cognitive impairment (n=13) [39, 41-43, 46, 48-51, 55-57, 65] than excluded people with these conditions (n=7).[20, 38, 44, 47, 61, 63, 64]

Participant mortality

Mortality was reported in 19 studies at nine different time points, ranging from 'in the ICU'[38, 40] to one year post intervention. [46, 55, 62] In these studies, 2090 participants died (23%). Mortality rates ranged from 1% in three studies[20, 47, 61] to 100% in the palliative care unit study.[49] There were 596 participant deaths in 18 studies reporting mortality that were conducted outside of a specialist palliative care setting (12%). High mortality was reported for intervention and control medical unit participants at eight weeks (22.1% vs 19.37%; [50] 33% vs 37% for delirious patients[51]) and at six months (33.8% vs 30.9%);[39] and at one year for older (≥65) traumatic hip fracture patients (33% vs 22%).[46] Six of the 19 studies measuring mortality excluded patients expected to die; despite this exclusion criteria, 134 participants of these six studies subsequently died during the study period (12%).[20, 44, 46, 52, 58, 62] Fifteen studies reported 21 comparative mortality rates,[20, 38-40, 45, 46, 50-55, 61-63] only two

of which reported significantly less mortality in intervention cohorts compared to controls,[54, 61] with one (at day 7 in hospital) not sustained at 30 days in hospital.[61]

Study approaches to people requiring palliative care

By examination of these data we identified only one study that explicitly reported outcomes for participants requiring palliative care (n=1).[49] Using the GSF PIG, we identified another four studies that reported primary or sub-group effectiveness outcomes for older people likely to require palliative care due to the presence of frailty, dementia, cancer and comorbidity.[42, 52, 53, 57] All five studies were of interventions to prevent delirium. Twenty-two studies either explicitly or resultantly excluded groups of people requiring palliative care (76%). [20, 38, 39, 41-44, 46-48, 50-52, 55, 58-65] Yet, through our interpretation of reported diagnoses, levels of comorbidity, frailty and mortality (signified with a † in Table 2), we also identified that people requiring palliative care were present in 21 studies that did not specifically characterise them or report their outcomes (72%). [20, 38-41, 43, 45-48, 50, 51, 54-56, 58, 61-63, 65] Figure 3 presents these findings diagrammatically.

(**Insert Table 2**: **Study inclusion and exclusion criteria and participant diagnoses, illness severity and mortality**)

* Statistically significant difference $^{\Delta}$ Intervention and control participants combined $^{\alpha}$ Rounded to nearest whole number † Interpreted as indicating need for palliative care

Illness severity measures: Higher scores represent higher illness severity. **AIS** Abbreviated Injury Scale, **APACHE II** Acute Physiology and Chronic Health Evaluation (scores 0-71), **ASA** American Society of Anesthesiologists physical status classification (I: normal healthy patient - VI: a declared brain-dead patient whose organs are being removed for donor purposes), **BDRS** Blessed Dementia Rating (scores 0-28, cut-off for impairment > 4), **CCI** Charlson Comorbidity Index (scores 0-37), **CIRS-G** Cumulative Illness Rating Scale–Geriatrics (scores 0-56), **CSI** Clinical severity of illness (1 (mild) - 9 (moribund)), **GCS** Glasgow Coma Scale (scores 3-15; scores 3-8 = coma), **GDS-15** 15-item Geriatric Depression Scale (≥6 = suggests depression and need for assessment, ≥11 = depression/severe depression), **ISS** Injury Severity Score (scores 1-75), **MEWS** Modified Early Warning Score (score ≥5 is statistically linked to increased likelihood of death or admission to an intensive care unit), **RIFLE** (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease categories), **SAPS 3** Simplified acute physiology score **(scores** 0-217), **SOFA** Sepsis-related Organ Failure Assessment (scores 0 to 24). **Other abbreviations: ADL** activities of daily living, **AF** atrial fibrillation, **Ca** cancer, **CAM** Confusion Assessment Method, **CAM-ICU** Confusion Assessment Method for the Intensive Care Unit, **CI** cognitive impairment, **CKD** Chronic Kidney Disease, **COPD** chronic obstructive pulmonary disease, **CVD** cardiovascular disease, **CVA** cerebrovascular accident, **DM** diabetes mellitus, **ED** Emergency Department, **GI** gastrointestinal, **HF** heart failure, **hrs** hours, **HT** hypertension, **I/C** intervention/control**, ICU** intensive care unit, **IHD** ischaemic heart disease**, IQR** interquartile range, **MI** Myocardial Infarction, **MMSE** Mini-Mental State Examination, **NR** not reported, **O/A** on admission, **OP** osteoporosis, **PVD** peripheral vascular disease, **RASS** Richard Agitation Sedation Scale, **RF** renal failure, **SD** standard deviation, **SICU** surgical intensive care unit, **TIA** transient ischemic attack, **UTI** urinary tract infection.

Figure 3: Study approaches to people requiring palliative care
NB: Combined percentages do not add up to 100% as studies simultaneously excluded and reported people requiring palliative care.

Effectiveness outcomes for people requiring palliative care

Overall, 20 studies reported that the intervention was effective according to at least one primary outcome (69%)[20, 38-42, 44-46, 51, 54-57, 59-64]

The one study explicitly focused on preventing delirium in people receiving palliative care (patients with terminal cancer) tested three primarily nurse-delivered intervention components for orientation, informing family, and assessment of medication risk factors plus querying physicians about changes to medication and found no statistically significant difference in delirium incidence (p= 0.66, OR 0.94), severity or duration between intervention and control sites.[49]

Outcomes of four participant groups that we identified as requiring palliative care were as follows:

A delirium prevention RCT of a geriatric liaison intervention of comprehensive assessment, cognitive and physical activity, hearing, vision and nutrition for frail elderly cancer patients undergoing surgery for a solid tumour reported no significant difference between delirium incidence in intervention and control groups (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29–1.35).[53]

A delirium prevention RCT of geriatric consultation and multiple care components (Table 3) performed analysis for the sub-group pf people with dementia within a perioperative hip fracture population, reporting a non-statistically significant reduction in delirium incidence in the intervention group compared with control (n=13 (62%) vs. n=20 (69%) p=0.6).[42]

A delirium prevention before-after study of orientation and communication strategies for patients with dementia in a French acute geriatric unit reported a 66% relative risk reduction of delirium in the after cohort (RRR 0.34 IC 95% 0.15–0.78).[57]

A delirium prevention before-after study of delirium/cognitive screening, comprehensive assessment, cognitive and physical activity, nutrition, falls prevention, medication review and staff education in frail elderly surgical patients found no statistically significant

difference in incidence of delirium (11% vs 10% p=0.945) or cognitive decline (15% vs 12% p=0.431) in the before group compared with the after.[52]

Due to heterogeneity of study interventions and measures (Table 2), we did not conduct meta-analysis of these effectiveness outcomes.

Types of outcomes measured in the included studies

Twenty-nine different outcomes were measured overall (Figure 4). There were nine different primary outcomes, the most frequent was delirium incidence (n=21). [20, 38, 39, 41-46, 48, 49, 52, 53, 56-61, 63, 64] Of the 22 different secondary outcomes, the most often reported was length of ICU or hospital stay (n=16).[38-43, 45, 46, 48, 50, 51, 53-56, 62]

Figure 4: Types and rates of outcomes measured

Feasibility outcomes

Intervention components

The interventions consisted of 24 components overall, varying in type and number per study (1-15) (M=6.3 SD ±4) (Table 3). The type and number of strategies in each component also varied (data not reported here).

Eighteen multicomponent *prevention* interventions most often included strategies for: cognitive activity (n=15);[20, 39, 41, 43-45, 49, 52, 53, 56, 57, 59, 61, 63, 64] physical activity (n=9);[20, 39, 43, 45, 52, 53, 59, 63, 64] hearing (n=9);[20, 39, 41, 44, 45, 53, 56, 61, 63] vision (n=9);[20, 39, 41, 44, 45, 53, 56, 61, 63] sleep-wake cycle preservation (n=8);[20, 40, 41, 45, 59, 61, 63, 64] nutrition (n=8);[41, 44, 45, 52, 53, 59, 61, 63] staff education; [39-41, 52, 59, 61, 63, 64] and hydration (n=7). [20, 41, 44, 45, 59, 61, 63] These components largely correspond to those of the original HELP study.[20]

Components of six delirium *prevention and treatment* interventions were more diverse (M=8), with staff education (n=4),[38, 48, 54, 55] staff changes (n=3) [48, 54, 55] and strategies for pain (n=3) most often included.[42, 48, 55]

The most common components of three delirium *treatment* interventions were cognitive activity (n=3);[50, 51, 62] physical activity (n=3);[50, 51, 62] hearing (n=3);[50, 51, 62] vision (n=3);[50, 51, 62]

sleep-wake cycle preservation (n=2);[50, 62] and environmental changes (e.g. adjustments to lighting and noise) (n=2).[51, 62]

Overall, multicomponent interventions also often included: family involvement (e.g. information/education about delirium, increased family presence) (n=9); [38, 45, 49-51, 56, 58, 59, 61] environmental strategies (n=9); [38, 40, 42, 45, 50, 51, 61, 62, 64] and comprehensive assessment (n=8).[42, 46, 50-53, 55, 61] Pharmacological strategies (e.g. medication reviews and alerts, protocols for pain and sedation strategies) were present in half of the multicomponent interventions (n=12).[38, 40-42, 45, 48, 49, 52, 55, 59, 61, 64]

The three *single component* interventions were blood transfusion,[65] bright light therapy[60] and earplugs at night.[47]

The five studies that reported effectiveness outcomes for our sample of interest addressed: cognitive activity,[42, 49, 52, 53, 57] physical activity,[42, 52, 53] comprehensive assessment,[42, 52, 53] hearing,[42, 53] vision,[42, 53] nutrition,[42, 52, 53] pharmacological strategies,[42, 49, 52] environmental strategies[42, 57] family involvement,[49] staff changes,[42] pain,[42] medical complications,[42] oxygen,[42] staff education,[52] falls prevention[52] delirium/cognitive screening[52] and bladder/bowel function[42] (Figure 5).

Intervention delivery

Specialist geriatric clinicians or teams led almost half of the interventions, as either consultants or directly (n=12).[20, 39, 42, 45, 46, 50-53, 55, 62, 63] Interventions were delivered by interdisciplinary teams (n=5),[20, 38, 45, 46, 55] physicians and nurses (n=3),[49-51] nurses alone (n=3),[47, 48, 61], physician, nurse and physiotherapists (n=2),[59, 64] family members (n=2),[56, 58] and physiotherapists and allied health assistants (n=1).[43] Volunteers delivered part or all of the intervention in four studies.[20, 41, 44, 52] Three studies did not report who delivered the intervention, including two single component interventions. [57, 60, 65] Most studies (n=25) wholly or partly tailored components and strategies to patients' individual needs (Table 3).

(Insert Table 3 Intervention characteristics here)

Abbreviations: ICU Intensive Care Unit, **NR** Not reported, **OA** On admission, **OT** Occupational therapist, **PT** physiotherapist **Component codes: C** Cognitive activity, **E** Physical activity, **H** Hearing, **V** Vision, **P** Sleep-wake cycle preservation, **W** Hydration, **S** Staff education, **F** Family involvement, **N** Nutrition, **Pa** Pain, **O** Oxygen, **L** Falls prevention, **G** Staff changes, **B** Bladder/bowel, **J** Environment/lighting/noise, **CA** Comprehensive assessment, **BT** Blood transfusion, **Z** Address medical complications, **PE** Patient education, **Ph** Physiological monitoring, **K** Pharmacological

Figure 5: Types and rates of intervention components, including for sample of interest
Code: P Delirium prevention studies, **P & T** Combined delirium prevention and treatment studies, **T** Delirium treatment studies, **S of I** Sample of interest

Adherence

Eighteen studies reported adherence to intervention strategies, using different methods and levels of detail (Supplementary Table 1). Almost all reported less than 100% adherence, with the exception reporting 100% geriatric nurse compliance with the "semi-structured protocol".[62] The palliative care unit study reported 89.7% overall adherence to the study protocol.[49] Three studies compared adherence to intervention strategies with that for control participants and reported that usual care sometimes mirrored some intervention strategies.[46, 50, 55] Two studies reported reasons for non-adherence: pharmacological sedation, coma and absence of a relative in the palliative care unit study; [49] and patient refusal or unavailability, staff member unavailability, and medical contraindications in the original HELP study.[20]

Study modifications

Two studies modified the intervention in the pilot phase, including changes in staff education and practice change materials,[39] and providing study information to family on admission rather than waiting until the researcher was present. [58] The palliative care unit study modified the primary outcome measure by not substituting the CRS for the CAM, due to CAM completion delays and poor completion rates (39% of participants) caused by "the challenge of conducting the baseline CAM structured interview in the last days or hours of life".[49]

Acceptability outcomes

Adverse effects

No study reported systematic processes of attribution of adverse effects to the intervention. Ten studies reported adverse events related to hospitalisation rather than the intervention [38, 44, 51-53, 55, 56, 62, 63] (Figure 4 and Supplementary Table 2). No study reported statistically significant increased adverse events for intervention participants. Two simply stated that the intervention had no adverse effects.[20, 43] A RCT,[55] a controlled trial [63] and a before-after study [62] reported statistically significant reductions in some adverse events for intervention participants: falls,[55] physical restraint,[62, 63] pressure ulcers,[55, 62] infection,[55, 62] and sleeping problems.[55]

Patient, family, clinician and volunteer subjective experiences

No study reported patients' subjective experiences of intervention (Supplementary Table 3). A survey of family caregiver's satisfaction with intervention and care for delirious patients within one study found most experienced moderate to high levels of distress (72%), believed that the environment and intervention helped the patient's recovery (86.6% and 83.5%, respectively) and that the three most useful strategies were activity, reality orientation and thrice-daily mobilisation.[62] A before-after study of older medical and surgical inpatients interviewed patients, volunteers, nurses and physicians and analysed meeting minutes to assess intervention integration in clinical practice, with minimal details of analysis methods and findings provided. [52] Four studies reported multidisciplinary and expert input during intervention development.[39, 40, 45, 61] The RCT of nocte earplugs in the ICU stated in the discussion that some participants preferred not to use them in order to remain "in direct contact with their environment". [47] No studies reported measures of patient distress related to delirium (Figure 5).

Discussion

This review found that studies of non-pharmacological delirium interventions frequently excluded and under-characterised people requiring palliative care and subsequently their outcomes were infrequently reported. The likely reasons for these findings and how to address barriers to inclusion and report characteristics and outcomes for this patient sub-group in future research are discussed.

With regards to inclusion, this review identified a selection bias against people requiring palliative care through exclusion of people expected to die (using various prognoses and terminology) and also of those with greater acuity or severity of illness, particular diagnoses and with cognitive, sensory and/or communication impairments. These exclusions were rarely explained or justified and often seemingly arbitrary. Nor were they consistent across the studies. These exclusions represented people highly at risk of delirium.[1, 6] This finding reflects those of other reviews that identified selection biases against people with dementia in geriatric research[76] and older people from clinical trials in oncology.[77] Reasons for the exclusions identified in our review are likely to be multifactorial. One factor may be assumptions that the interventions were not appropriate, possible or likely to be effective for people requiring palliative care, as indicated by the two studies which justified the exclusion of patients with a terminal condition and requiring comfort care as that the intervention would be unlikely to benefit them.[41, 44] Historical views that people requiring palliative care are separate from the wider hospital population, rather than universally and always within it, may also have influenced some exclusion decisions.[78, 79] There are also pragmatic challenges to ensuring informed consent and completion of study measures when patients are frail, expected to decline, and have pre-existing cognitive and sensory impairments. However, these challenges may be overcome through a variety of research strategies, such as proxy, opt out and advance consent methods, early contact, tailoring of interventions and messaging to patients and family, adequate research resources and governance, and cluster designs.[26, 27, 80, 81] Outcomes such as days alive without delirium or coma may promote the inclusion of more severely ill patients in future delirium research, because consciousness is pre-requisite for delirium measurement.[40, 82] Brief and

observational delirium diagnostic tools that can be validly used with patients with cognitive, sensory and communication impairment are also available.[83-86]

Despite most studies excluding certain groups of people likely to require palliative care, unsurprisingly we identified that they were indeed present, despite under-reporting of their characteristics and outcomes. One reason it was difficult to retrospectively distinguish this sub-group for the purposes of ascertaining their outcomes in this review was that the studies reported participants' diagnoses, illness severity, and mortality using different measures, time-points, methods and degrees of detail. While identifying inpatients with palliative care needs in hospital is challenging and an uncertain science, both retrospectively and prospectively, there are ways it can be achieved. [29, 87-89] In addition to the GSF PIG which we applied in this review, [29] the Palliative Care Needs Assessment Tool [90] and the Supportive and Palliative Care Indicators Tool (SPICT) [91] can be used to identify which patients are at risk of deteriorating and dying in hospital. Other studies suggest identifying patients with palliative care needs through the presence of life-threatening illness coupled with receipt and acceptance of care focused on supporting quality of life, [87] or retrospectively though the use of death registration data. [89] Such methods could be used in delirium intervention research in settings where mortality is high, such as intensive care units, where existing illness severity measures focus on acuity and intensity of intervention and, despite having some prognostic utility, were never designed to identify a patient's need for palliative care.[67, 74, 92]

Better characterisation of people requiring palliative care in studies of non-pharmacological interventions for delirium would help to build evidence of their outcomes in two ways.

Firstly, it would allow sub-group analysis to be performed and reported in future studies in any setting. This is important because the question of whether delirium can be prevented and treated through non-pharmacological means was not definitively determined for this population by this review. The multi-site palliative care unit study had the greatest number of participants and reported good overall adherence to the study protocol; [49] however, the only core care domain [21] was cognitive activity, consisting of nurses orientating patients to time, person and place each shift. Planned use of the CAM was not accomplished and the

substituted screening tool[93] was not a validated tool for delirium diagnosis or severity. All participants had 'terminal' cancer and died within 90 days of admission and thereby were not fully representative of people requiring inpatient palliative care, including in specialist units[49], not all of whom will die within three months. Only one geriatric unit study of people with dementia reported reduced delirium incidence; however, the report lacked detail, including of analysis methods.[57] The remaining three studies were focused on frail elderly patients with cancer, dementia, hip fracture and comorbidity following surgery,[42, 52, 53] a level of intervention and delirium risk that many people requiring palliative care would not undergo. Lastly, we found no studies focused on non-pharmacological interventions to treat delirium in people requiring palliative care, highlighting the particular need to research this challenging area of clinical care.

Secondly, better recognition of people requiring palliative care in delirium research would heighten awareness of their needs, which in turn would instigate consideration of outcomes that are most meaningful to them. Reducing delirium incidence, duration and severity, length of admission and mortality were the foci of the included studies. While worthwhile aims at any point in the illness trajectory, more person-centred outcomes, such as reduction of delirium related distress, and improved patient and family caregiver experiences of decision making, respect and dignity, and quality of life, were almost completely absent. [5, 94] Measuring these additional outcomes, which are highly valued by patients and family caregivers,[95, 96] would enrich this field of research and is achievable through both quantitative and qualitative methods. Adverse effects of intervention will also be important to systematically measure in future trials, given that patients with cognitive impairment have increased vulnerability to harm in hospital.[97]

Lastly, this review allowed an interpretation that many intervention components are feasible for people requiring palliative care by virtue of their delivery to elderly, frail and/or critically ill patients with and without delirium in the included studies. However, we suggest that studies measuring the feasibility of components of the original HELP intervention [20] that were subsequently found to be effective for other older hospitalised patients i.e. those targeting cognitive and physical activity, sleep, hearing, vision and hydration,[21-23] are necessary next steps within delirium research programs in specialist palliative care settings.

Limitations and strengths

A limitation of this review was that only English language studies were included. Another limitation was that our retrospective identification of people requiring palliative care was not sufficient to definitively determine outcomes for this patient sub-group; therefore this review makes only recommendations for future research, not clinical practice. A strength of this review was our systematic approach adhering to PRISMA.[30]

Conclusion

This review found that studies of non-pharmacological delirium interventions have excluded, poorly characterised and infrequently reported outcomes for people requiring palliative care. Based on these findings, we suggest new approaches to generate evidence for delirium interventions in this important patient sub-group. First, randomised controlled trials of non-pharmacological interventions to prevent and treat delirium are needed in specialist palliative care settings, with feasibility studies required before trials of effectiveness. Interventions should be based on those implemented and proven effective for older patients, especially those who were frail and severely ill with comorbidity. Second, broad inclusion criteria, justified exclusions, and tailoring in future inpatient trials of non-pharmacological delirium interventions would promote representative study populations. Third, systematic characterisation of the sub-groups of people requiring palliative care would allow their specific outcomes to be reported. Last, additional outcomes related to patient and family subjective experience, goals of care and quality of life would enhance the relevance of delirium research in inpatient settings where people are cared for at the end of life.

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Inclusion, characteristics and outcomes of people requiring palliative care in studies of non-pharmacological interventions for delirium: a systematic review

Abstract

Background

Delirium is common, distressing, serious and under-researched in specialist palliative care settings.

Objectives

To examine whether people requiring palliative care were included in non-pharmacological delirium intervention studies in inpatient settings, how they were characterised, and what their outcomes were.

Design

Systematic review (PROSPERO 2017 CRD42017062178).

Data sources

Systematic search in March 2017 for non-pharmacological delirium intervention studies in adult inpatients. Database search terms were 'delirium', 'hospitalisation', 'inpatient', 'palliative care', 'hospice', 'critical care', 'geriatrics'. Scottish Intercollegiate Guidelines Network methodological checklists guided risk of bias assessment.

Results

The 29 included studies were conducted between 1994-2015 in diverse settings in 15 countries (9136 participants, mean age 76.5 years [SD 8.1], 56% women). Most studies tested multicomponent interventions (n=26) to prevent delirium (n=19). Three-quarters of the 29 included studies (n=22) excluded various groups of people requiring palliative care; however, inclusion criteria, participant diagnoses, illness severity and mortality indicated their presence in almost all studies (n=26). Of these, 21 studies did not characterise

participants requiring palliative care or report their specific outcomes (72%), four reported outcomes for older people with frailty, dementia, cancer and comorbidities, and one was explicitly focused on people receiving palliative care. Study heterogeneity and limitations precluded definitive determination of intervention effectiveness and only allowed interpretations of feasibility for people requiring palliative care. Acceptability outcomes (intervention adverse events and patients' subjective experience) were rarely reported overall.

Conclusion

Non-pharmacological delirium interventions have frequently excluded and under-characterised people requiring palliative care and infrequently reported their outcomes.

Key words

Clinical trial, Delirium, Hospice, Inpatient, Palliative Care, Review

Key statements

What is already known about the topic?

- Delirium is a distressing and serious neurocognitive condition that frequently occurs for patients in palliative care inpatient settings.
- In contrast to other hospital settings, there is limited evidence to guide non-pharmacological intervention to prevent and treat delirium in palliative care inpatient settings.

What this paper adds

- This review found that various groups of people requiring palliative care were excluded from three-quarters of non-pharmacological delirium intervention studies in inpatient settings; despite this, they were present in most studies and their outcomes were reported in five.
- Non-pharmacological delirium interventions appear feasible for people requiring palliative care yet there is no definitive evidence they are effective or acceptable for this inpatient group.

Implications for research

- Phase II and III randomised controlled trials of non-pharmacological interventions to prevent and treat delirium are needed in specialist palliative care settings.
- Adaptations to future trials of non-pharmacological delirium interventions in other inpatient settings are needed to promote representative study populations and allow outcomes for sub-groups of people requiring palliative care to be reported.
- Additional outcomes related to patient and family subjective experience, goals of care and quality of life would enhance the relevance of delirium intervention research in inpatient settings where people are cared for at the end of life.

Introduction

Delirium is a serious complication of medical illness and hospitalisation.[1] The condition is characterised by acute disturbances to attention, awareness and cognition, has multifactorial aetiology, and variously affects memory, language and visuospatial ability, orientation and perception.[2] Affected persons often experience feelings of fear, humiliation, confusion and disconnection from others.[3, 4] Family members' experience distress when delirium causes sudden changes in behaviour and decline in the person they love.[5 6] Patients who experience an episode of delirium during hospitalisation experience many poorer outcomes, including being more likely to die.[1, 7, 8]

Delirium most often occurs in people with older age, advanced or severe illness and/or pre-existing cognitive impairment. Hospital-wide, one in five patients have delirium,[9] with occurrence higher again in intensive, geriatric and palliative care units.[1, 6] Studies of delirium epidemiology in palliative care inpatient units that screened patients at least daily reported incidence of 33–45% and prevalence of 58-88% in those who died.

Development of delirium guidelines[1, 10-13] policy[14] and international advocacy[15] indicate growing awareness of the seriousness and prevalence of delirium and importance of evidence based care for hospitalised patients.[16, 17] There now is sufficient evidence to implement non-pharmacological interventions for delirium in certain hospital settings.[18, 19] For example, reviews of studies of multicomponent interventions addressing physical and cognitive activity, sleep, hearing, vision and hydration, as in the original Hospital Elder Life Program (HELP) study,[20] reported reduction in incident delirium in older hospitalised patients.[21-23] Reduction in length of hospital stay and improvement in return to independent living were also demonstrated.[22]

In contrast, guideline recommendations for non-pharmacological interventions as the first approach to prevent and treat delirium during advanced illness and at the end of life are not evidence based.[10, 17, 24] A recent scoping review reported the need to generate evidence to inform clinical care in palliative care settings and populations, for non-pharmacological interventions in particular.[25] Poorer outcomes with antipsychotics,[26] and over-sedation

when benzodiazepines were given for agitated delirium,[27] in two recent trials in specialist palliative care settings also highlight the need to establish 'drug-free' ways to prevent and relieve the difficulties of delirium at the end of life.

In response, the authors established the '*Studies to Understand and Improve Delirium Care in Palliative Settings*' international collaborative (SUNRISE) to generate high-quality delirium research in palliative care. We identified the need to inform our future trials in palliative care through a review of studies of non-pharmacological interventions for delirium conducted in a wide range of inpatient settings. This wide review was premised on our clinical experience and knowledge that many hospitalised patients have advanced and/or serious illness, frailty and high comorbidity and consequently much in common with patients in specialist palliative care settings, especially those in intensive care, medical and geriatric units where rates of delirium are similarly high. [28, 29] Based on this premise, our specific objectives were to examine whether people requiring palliative care were included in non-pharmacological delirium intervention studies in various inpatient settings, how these participants were characterised, and whether the non-pharmacological interventions were effective, feasible and/or acceptable for them.

Methods

Design

Systematic review of the literature, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[30]

Participants/settings

Adults (≥18 years) receiving inpatient hospital or hospice care. In this review, we refer to 'hospice' as an inpatient facility with the primary function to provide specialist palliative care to people with life-threatening illness, and analogous to a palliative care inpatient unit.

Search strategy

In March 2017, we searched MEDLINE, Embase, CINAHL, PsycINFO, Cochrane Library and Web of Science with the following search terms in MEDLINE: Delirium AND Hospitalization

OR Inpatient OR Hospice AND Palliative Care OR Critical Care OR Geriatrics. Filters in Medline were: 1. Study types: clinical study, clinical trial all, comparative study, controlled clinical trial, meta-analysis, multicenter study, pragmatic clinical trial, randomised controlled trial, systematic review; 2. Peer reviewed journal and 3. Published from 1980 onward (when delirium was first included in the American Psychological Association (APA) Diagnostic and Statistical Manual (DSM-III).[31] We tailored search terms and filters to subsequent databases. We examined reference lists of relevant systematic reviews and meta-analyses identified in the search for additional eligible studies.

Inclusion/exclusion criteria

Studies included were primary reports of prospective trials (i.e. studies of an intervention with a comparator); with a primary objective to prevent or treat delirium through non-pharmacological intervention/s in adult patients in hospital or hospice unit settings; a primary outcome of delirium incidence, severity or duration; published in English in a peer-reviewed journal.

Studies excluded were reports of interventions for alcohol withdrawal delirium only; systematic reviews and meta-analyses of non-pharmacological delirium intervention/s; studies where the primary outcome was not participants' delirium status (e.g. process or cost effectiveness outcomes, validation of delirium tools); studies that did not use diagnostic criteria or a tool with established psychometric properties to measure delirium; protocols; and ongoing studies.

Study selection, data extraction and management

We imported search results into Endnote X7 software, removed duplicates and exported results to Covidence,[32] where three reviewers [IAD, LE, AH] independently applied eligibility criteria to titles and abstracts. Reviewers compared decisions about inclusion, documented reasons for exclusions at full text review and resolved discrepancies through discussion. Two reviewers [IAD, LE] extracted data according to the template for intervention description and replication (TIDieR) checklist and guide [33] into an Excel V15.28 spreadsheet. The lead reviewer [AH] contributed guidance, oversight and independent data checking.

Risk of bias assessment

Two reviewers [LE and AH] independently assessed each study for selection, performance, detection, attrition, confounding, and reporting biases according to the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklists[34] for controlled trials and cohort studies. Discrepancies were resolved through discussion.

Outcomes

To identify our sample of interest (i.e. people requiring palliative care), we examined study inclusion and exclusion criteria, participant diagnoses (including severity or staging), and mortality. We assessed eligibility criteria and diagnoses against the Gold Standards Framework Proactive Identification Guidance (GSF PIG), a clinical tool to help identify people likely to need additional supportive (i.e. palliative) care in the last 12 months of life.[29] According to the GSF PIG, these people are those with life-threatening conditions, including illnesses that are advanced, progressive, incurable and/or likely to cause acute crises; frailty and co-morbidities; and sudden catastrophic events.

Previous reviews have reported effectiveness outcomes of non-pharmacological delirium interventions for the entire study sample; [21-23] whereas this review focused on effectiveness, feasibility and acceptability outcomes of our sample of interest. We examined effectiveness according to each study's primary outcome and any sub-group analysis for our sample of interest. We assessed feasibility by examining intervention characteristics, adherence and study modifications, and acceptability through intervention-related adverse effects and patient, family, clinician and volunteer subjective experiences of the interventions.

Synthesis and analysis plan

We generated tables, text and graphs to report study characteristics, participants, interventions and outcomes. Data transformation and descriptive numerical analyses were performed using Excel. We planned to perform subgroup meta-analysis using Review Manager Analyses software [35] of intervention effectiveness if we could definitively distinguish our sample of interest and if interventions and comparators and measures were comparable.

Updated search

We updated the search prior to publication in February 2019 and identified two new eligible papers published after the original search date.[36, 37] There were not incorporated as neither paper altered the conclusions of the review.

Results

The original database search strategy generated 4300 records. After removing 35 duplicates and 4169 records through title and abstract screening, we reviewed 69 full text papers and excluded 48. We included another eight through reference list searching, resulting in 29 papers reporting 29 studies for inclusion (Figure 1).

(Insert Figure 1 PRISMA Flow Diagram here)[30]

Study characteristics

The 29 studies were conducted between 1994-2015 across 15 countries: six in the US,[38 39 40 41 42 20] three each in Australia,[43 44 45] Belgium,[46-48] and Canada,[49-51] two each in the Netherlands[52, 53] and Sweden,[54, 55] and one each in Chile,[56] France,[57] Ireland,[58] Italy,[59] Japan,[60] Korea,[61] Singapore,[62] Spain,[63] UK,[64] and the US/Canada[65] (Table 1).

Study designs were before/after studies (one with an additional concurrent arm[62]) (n=11),[38-41, 44, 45, 48, 52, 57, 62, 64] randomised controlled trials (RCTs) (n=10),[42, 43, 47, 50, 51, 53, 55, 56, 61, 65] non-randomised controlled trials (one with matched participants[20]) (n=5),[20, 46, 54, 59, 63] a quasi-experimental study,[49] a pilot randomised controlled trial,[60] and a comparative time series study.[58]

Services and settings were medical (n=10),[20, 41, 43, 50-52, 54, 56, 59, 63] geriatric (n=7),[39, 44, 55, 57, 59, 62, 63] medical and/or surgical intensive care (n=6),[38, 40, 47, 58, 61, 64] perioperative hip fracture (n=6),[42, 45, 46, 48, 55, 65] other perioperative (n=3) [52, 53, 60] and palliative care and hospice units (n=1), [49] with eight studies involving more than one service.[47, 52, 55, 58, 59, 61, 63, 64]

Most studies tested multicomponent interventions (n=26) and aimed to prevent delirium in non-delirious participants (n=19) (Table1). Six studies aimed to prevent and treat delirium [38, 42, 48, 54, 55, 65] three were treatment only studies.[50, 51, 62]

(Insert Table 1 Study characteristics here)

Code: P Prevention, **T** Treatment, **RCT** Randomised controlled trial, **CTS** Comparative time series, **B/A** Before–after study, **CT** Controlled trial, **ICU** Intensive Care Unit, **NR** Not reported, **MC** Medical Centre, **M** Multicomponent, **PRCT** Pilot RCT, **QE** Quasi-experimental, **S** Single component

[Δ] Numbers signify the domains in which the study was assessed as having **low risk of bias**: 1 = Representative study sample; 2 = Concealed allocation; 3 = Random sequence generation; 4 = Blinded participants and intervention personnel; 5 = Blinded outcome assessors; 6 = Valid, reliable delirium measures; 7 = <20% sample lost to analysis; 8 = Intention to treat analysis; 9 = Confounders accounted for; 10 = Only *a priori* outcomes reported

Risk of bias assessment

Almost all studies were assessed as having at least one form of selection bias (n=28). The exception was a Chilean RCT of a prevention intervention where family members delivered cognition, vision, and hearing strategies to patients.[56] Eight RCTs minimised internal selection bias through concealed allocation and random sequence generation.[42, 43, 47, 50, 53, 55, 56, 65] There was high risk of performance bias in all studies, due to the inherent difficulty of blinding non-pharmacological interventions: one RCT blinded participants to their allocation,[43] and no studies blinded those performing the intervention. Detection bias was minimised in eight studies through blinded outcome assessors combined with valid, reliable delirium measures.[42, 43, 47, 50, 51, 53-55] Although we excluded studies that did not use delirium diagnostic criteria and/or a tool with established psychometric properties, three studies were assigned uncertain risk of detection bias due to retrospective assignment of delirium status when the Confusion Assessment Method (CAM) was not performed during weekends in two before-after studies;[41, 45] and when delirium incidence was reported as a mean rather than a proportion in a comparative time series study.[58] High risk of detection bias was assigned to a delirium prevention study in seven Canadian palliative care units due use of a screening tool, the Confusion Rating Scale (CRS) to measure delirium incidence, severity and duration.[49] Six studies had low risk of attrition bias.[42, 43, 50, 55, 56, 63] Confounders were accounted for in 17 studies.[20, 39, 40, 42, 46, 47, 49-52, 54, 55, 58, 59, 61, 63, 65] Most studies (n=22) reported only *a priori* outcomes,[20, 38-43, 46, 48, 50-53, 55-57, 60-65] which we assessed by information provided within the papers rather than through examination of trial registrations or published protocols, which no studies cited.

Figure 2 presents overall risk of bias in the included studies.

(Insert Figure 2 Overall risk of bias graph here)

Figure 2: Overall risk of bias

Participant characteristics

There were 9136 participants (n=4553 in intervention arms) across the 29 studies (Table 2). Sample sizes ranged from 15-1516 participants. Participants' overall mean age (excluding two studies that reported only age range or median) [48, 58] was 76.5 years (SD ± 8.1). There were more female participants (56%) than male.

Inclusion and exclusion criteria

Inclusion

Most studies (n=19) included only patients aged 65 years and older (Table 2). Twenty-two studies included consecutively admitted patients, 16 of which further required certain physical conditions to be present (e.g. frailty,[53] hip fracture,[42, 45, 46, 48, 55, 65] anemia,[65] dementia,[57] advanced cancer,[49] oesophageal cancer surgery[60]). Five studies included only patients with risk factors for delirium[20, 44, 52, 56, 63] and three included only patients with delirium.[50, 51, 62] The study in seven Canadian palliative care units (hereafter termed the 'palliative care unit study') included only patients with terminal cancer, defined as dying within 90 days of admission which was retrospectively identified. This study had the largest sample of all the studies (n=1516, 17%).[49]

Exclusion

Twenty-three studies excluded patients on various diagnostic grounds (Table 2). These were stroke or cerebrovascular accident (CVA), moderate-severe traumatic brain injury or coma (n=9);[20, 38, 43, 48, 50, 51, 59, 62, 63] dementia or prior cognitive impairment (n=7);[20, 38, 44, 47, 61, 63, 64] psychiatric disorders or alcohol/drug addiction (n=6);[43, 44, 59-61, 64] pathological fracture (n=4);[46, 48, 55, 65] poly- or multiple trauma (n=2);[46, 48] neurologic diagnosis/neurosurgical (n=2);[61, 64] metastatic cancer or referred to oncology services (n=2);[42, 50] and others (myocardial infarction,[65] severe renal failure,[55] brain concussion,[48] history of sleep pathology,[64] severe rheumatoid arthritis [55] and severe hip osteoarthritis[55]).

Fifteen studies excluded patients with impaired verbal communication or who were otherwise unable to complete study assessments.[20, 38, 39, 41, 43, 46, 48, 50, 52, 53, 59, 61-63, 65] Six studies excluded patients with hearing and/or visual impairment.[46-48, 60, 61, 64] Three studies excluded patients isolated for infection.[43, 61, 62]

Eight studies explicitly excluded patients expected to die, using the following terms: "terminal diagnosis" or "terminal illness" (n=3),[20, 58, 62] "terminal condition and receiving comfort care" (on the basis that they were unlikely to benefit from the intervention) (n=2),[41, 44] "life expectancy less than six months",[46] "metastatic cancer or comorbid illnesses likely to reduce life expectancy to less than six months",[42] "death expected within 24 hours",[43] and "dangerously ill".[62]

Two studies excluded participants who subsequently died from analysis;[51, 52] a delirium prevention study in elderly care wards excluded 70% of 2162 admitted patients due to being "too unwell"; [39] and another study excluded patients with "deterioration of condition".[60]

The palliative care unit study excluded patients who lived for more than 90 days or who were still alive at discharge from analysis.[49]

Characterisation of study participants

Participant diagnoses and illness severity

Reporting of participant diagnoses, illness severity and mortality varied. Fifteen studies reported co-morbid diagnoses, twelve reported only primary diagnoses, and four reported both (Table 2). Diagnoses' categorisation varied. Studies rarely reported staging of diagnoses (n=2).[49, 56]

Sixteen studies reported illness severity for all participants using at least one measure, more often as a mean or median score (n=15)[20, 38, 43, 46, 47, 50, 52, 55, 56, 59, 61-65] than by categorising participants proportionally (n=6).[20, 39, 42, 47, 52, 62] The most frequently used illness severity measures were the Charlson Comorbidity Index (CCI)[66] (n=7; reported as: mean scores 2.3 - 3.3,[46, 50, 62] median 2,[43, 56] and scores of four or greater 19.8%[39] and 39%[42]); and the Acute Physiology And Chronic Health Evaluation II (APACHE II) [67] (n=6; mean scores 11.3-15.6).[20, 43, 59, 61, 63, 64] Two ICU studies that measured illness severity using the APACHE II reported

means scores (13.9-14.6) [61, 64] approximately equivalent to or less than those reported in three of four medical and geriatric unit studies (14.1-15.6).[20, 43, 59] Other measures were the Cumulative Illness Rating Scale–Geriatrics (CIRS-G) comorbidity and severity indexes;[52, 59, 68] American Society of Anesthesiologists physical status classification (ASA)[52, 65, 69]; Blessed Dementia Rating Scale;[20, 42, 70] Modified Early Warning Score (MEWS);[39, 71] Sepsis-related Organ Failure (SOFA);[47, 72] Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE);[47, 73] Simplified Acute Physiology Score (SAPS 3);[47, 74] and the 15-item Geriatric Depression Scale (GDS-15).[55, 75]

Three studies reporting comorbidities without the CCI reported: i. 60% had more than two comorbidities (diabetes, COPD, hypertension, myocardial infarction, other cardiovascular disorders, neurological disorders, cerebrovascular disorders, hearing and vision problems, memory problems in daily life, psychiatric disorders or musculoskeletal disorders);[53] ii. 72% had at least one co-morbid illness;[47] and iii. a mean of 2.7 comorbidities.[63]

Almost every diagnosis, sensory deficit and impairment that were exclusion criteria in some studies were reported in the overall study population (Table 2). For example, more studies reported participants with dementia or cognitive impairment (n=13) [39, 41-43, 46, 48-51, 55-57, 65] than excluded people with these conditions (n=7).[20, 38, 44, 47, 61, 63, 64]

Participant mortality

Mortality was reported in 19 studies at nine different time points, ranging from 'in the ICU'[38, 40] to one year post intervention. [46, 55, 62] In these studies, 2090 participants died (23%). Mortality rates ranged from 1% in three studies[20, 47, 61] to 100% in the palliative care unit study.[49] There were 596 participant deaths in 18 studies reporting mortality that were conducted outside of a specialist palliative care setting (12%). High mortality was reported for intervention and control medical unit participants at eight weeks (22.1% vs 19.37%; [50] 33% vs 37% for delirious patients[51]) and at six months (33.8% vs 30.9%);[39] and at one year for older (≥65) traumatic hip fracture patients (33% vs 22%).[46] Six of the 19 studies measuring mortality excluded patients expected to die; despite this exclusion criteria, 134 participants of these six studies subsequently died during the study period (12%).[20, 44, 46, 52, 58, 62] Fifteen studies reported 21 comparative mortality rates,[20, 38-40, 45, 46, 50-55, 61-63] only two

of which reported significantly less mortality in intervention cohorts compared to controls,[54, 61] with one (at day 7 in hospital) not sustained at 30 days in hospital.[61]

Study approaches to people requiring palliative care

By examination of these data we identified only one study that explicitly reported outcomes for participants requiring palliative care (n=1).[49] Using the GSF PIG, we identified another four studies that reported primary or sub-group effectiveness outcomes for older people likely to require palliative care due to the presence of frailty, dementia, cancer and comorbidity.[42, 52, 53, 57] All five studies were of interventions to prevent delirium. Twenty-two studies either explicitly or resultantly excluded groups of people requiring palliative care (76%). [20, 38, 39, 41-44, 46-48, 50-52, 55, 58-65] Yet, through our interpretation of reported diagnoses, levels of comorbidity, frailty and mortality (signified with a † in Table 2), we also identified that people requiring palliative care were present in 21 studies that did not specifically characterise them or report their outcomes (72%). [20, 38-41, 43, 45-48, 50, 51, 54-56, 58, 61-63, 65] Figure 3 presents these findings diagrammatically.

(**Insert Table 2**: **Study inclusion and exclusion criteria and participant diagnoses, illness severity and mortality**)

* Statistically significant difference $^{\Delta}$ Intervention and control participants combined $^{\alpha}$ Rounded to nearest whole number † Interpreted as indicating need for palliative care

Illness severity measures: Higher scores represent higher illness severity. **AIS** Abbreviated Injury Scale, **APACHE II** Acute Physiology and Chronic Health Evaluation (scores 0-71), **ASA** American Society of Anesthesiologists physical status classification (I: normal healthy patient - VI: a declared brain-dead patient whose organs are being removed for donor purposes), **BDRS** Blessed Dementia Rating (scores 0-28, cut-off for impairment > 4), **CCI** Charlson Comorbidity Index (scores 0-37), **CIRS-G** Cumulative Illness Rating Scale–Geriatrics (scores 0-56), **CSI** Clinical severity of illness (1 (mild) - 9 (moribund)), **GCS** Glasgow Coma Scale (scores 3-15; scores 3-8 = coma), **GDS-15** 15-item Geriatric Depression Scale (≥6 = suggests depression and need for assessment, ≥11 = depression/severe depression), **ISS** Injury Severity Score (scores 1-75), **MEWS** Modified Early Warning Score (score ≥5 is statistically linked to increased likelihood of death or admission to an intensive care unit), **RIFLE** (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease categories), **SAPS 3** Simplified acute physiology score **(scores** 0-217), **SOFA** Sepsis-related Organ Failure Assessment (scores 0 to 24). **Other abbreviations: ADL** activities of daily living, **AF** atrial fibrillation, **Ca** cancer, **CAM** Confusion Assessment Method, **CAM-ICU** Confusion Assessment Method for the Intensive Care Unit, **CI** cognitive impairment, **CKD** Chronic Kidney Disease, **COPD** chronic obstructive pulmonary disease, **CVD** cardiovascular disease, **CVA** cerebrovascular accident, **DM** diabetes mellitus, **ED** Emergency Department, **GI** gastrointestinal, **HF** heart failure, **hrs** hours, **HT** hypertension, **I/C** intervention/control**, ICU** intensive care unit, **IHD** ischaemic heart disease**, IQR** interquartile range, **MI** Myocardial Infarction, **MMSE** Mini-Mental State Examination, **NR** not reported, **O/A** on admission, **OP** osteoporosis, **PVD** peripheral vascular disease, **RASS** Richard Agitation Sedation Scale, **RF** renal failure, **SD** standard deviation, **SICU** surgical intensive care unit, **TIA** transient ischemic attack, **UTI** urinary tract infection.

Figure 3: Study approaches to people requiring palliative care
NB: Combined percentages do not add up to 100% as studies simultaneously excluded and reported people requiring palliative care.

Effectiveness outcomes for people requiring palliative care

Overall, 20 studies reported that the intervention was effective according to at least one primary outcome (69%)[20, 38-42, 44-46, 51, 54-57, 59-64]

The one study explicitly focused on preventing delirium in people receiving palliative care (patients with terminal cancer) tested three primarily nurse-delivered intervention components for orientation, informing family, and assessment of medication risk factors plus querying physicians about changes to medication and found no statistically significant difference in delirium incidence (p= 0.66, OR 0.94), severity or duration between intervention and control sites.[49]

Outcomes of four participant groups that we identified as requiring palliative care were as follows:

A delirium prevention RCT of a geriatric liaison intervention of comprehensive assessment, cognitive and physical activity, hearing, vision and nutrition for frail elderly cancer patients undergoing surgery for a solid tumour reported no significant difference between delirium incidence in intervention and control groups (9.4% vs. 14.3%, OR: 0.63, 95% CI: 0.29–1.35).[53]

A delirium prevention RCT of geriatric consultation and multiple care components (Table 3) performed analysis for the sub-group pf people with dementia within a perioperative hip fracture population, reporting a non-statistically significant reduction in delirium incidence in the intervention group compared with control (n=13 (62%) vs. n=20 (69%) p=0.6).[42]

A delirium prevention before-after study of orientation and communication strategies for patients with dementia in a French acute geriatric unit reported a 66% relative risk reduction of delirium in the after cohort (RRR 0.34 IC 95% 0.15–0.78).[57]

A delirium prevention before-after study of delirium/cognitive screening, comprehensive assessment, cognitive and physical activity, nutrition, falls prevention, medication review and staff education in frail elderly surgical patients found no statistically significant

difference in incidence of delirium (11% vs 10% p=0.945) or cognitive decline (15% vs 12% p=0.431) in the before group compared with the after.[52]

Due to heterogeneity of study interventions and measures (Table 2), we did not conduct meta-analysis of these effectiveness outcomes.

Types of outcomes measured in the included studies

Twenty-nine different outcomes were measured overall (Figure 4). There were nine different primary outcomes, the most frequent was delirium incidence (n=21). [20, 38, 39, 41-46, 48, 49, 52, 53, 56-61, 63, 64] Of the 22 different secondary outcomes, the most often reported was length of ICU or hospital stay (n=16).[38-43, 45, 46, 48, 50, 51, 53-56, 62]

Figure 4: Types and rates of outcomes measured

Feasibility outcomes

Intervention components

The interventions consisted of 24 components overall, varying in type and number per study (1-15) (M=6.3 SD ±4) (Table 3). The type and number of strategies in each component also varied (data not reported here).

Eighteen multicomponent *prevention* interventions most often included strategies for: cognitive activity (n=15);[20, 39, 41, 43-45, 49, 52, 53, 56, 57, 59, 61, 63, 64] physical activity (n=9);[20, 39, 43, 45, 52, 53, 59, 63, 64] hearing (n=9);[20, 39, 41, 44, 45, 53, 56, 61, 63] vision (n=9);[20, 39, 41, 44, 45, 53, 56, 61, 63] sleep-wake cycle preservation (n=8);[20, 40, 41, 45, 59, 61, 63, 64] nutrition (n=8);[41, 44, 45, 52, 53, 59, 61, 63] staff education; [39-41, 52, 59, 61, 63, 64] and hydration (n=7). [20, 41, 44, 45, 59, 61, 63] These components largely correspond to those of the original HELP study.[20]

Components of six delirium *prevention and treatment* interventions were more diverse (M=8), with staff education (n=4),[38, 48, 54, 55] staff changes (n=3) [48, 54, 55] and strategies for pain (n=3) most often included.[42, 48, 55]

The most common components of three delirium *treatment* interventions were cognitive activity (n=3);[50, 51, 62] physical activity (n=3);[50, 51, 62] hearing (n=3);[50, 51, 62] vision (n=3);[50, 51, 62]

sleep-wake cycle preservation (n=2);[50, 62] and environmental changes (e.g. adjustments to lighting and noise) (n=2).[51, 62]

Overall, multicomponent interventions also often included: family involvement (e.g. information/education about delirium, increased family presence) (n=9); [38, 45, 49-51, 56, 58, 59, 61] environmental strategies (n=9); [38, 40, 42, 45, 50, 51, 61, 62, 64] and comprehensive assessment (n=8).[42, 46, 50-53, 55, 61] Pharmacological strategies (e.g. medication reviews and alerts, protocols for pain and sedation strategies) were present in half of the multicomponent interventions (n=12).[38, 40-42, 45, 48, 49, 52, 55, 59, 61, 64]

The three *single component* interventions were blood transfusion,[65] bright light therapy[60] and earplugs at night.[47]

The five studies that reported effectiveness outcomes for our sample of interest addressed: cognitive activity,[42, 49, 52, 53, 57] physical activity,[42, 52, 53] comprehensive assessment,[42, 52, 53] hearing,[42, 53] vision,[42, 53] nutrition,[42, 52, 53] pharmacological strategies,[42, 49, 52] environmental strategies[42, 57] family involvement,[49] staff changes,[42] pain,[42] medical complications,[42] oxygen,[42] staff education,[52] falls prevention[52] delirium/cognitive screening[52] and bladder/bowel function[42] (Figure 5).

Intervention delivery

Specialist geriatric clinicians or teams led almost half of the interventions, as either consultants or directly (n=12).[20, 39, 42, 45, 46, 50-53, 55, 62, 63] Interventions were delivered by interdisciplinary teams (n=5),[20, 38, 45, 46, 55] physicians and nurses (n=3),[49-51] nurses alone (n=3),[47, 48, 61], physician, nurse and physiotherapists (n=2),[59, 64] family members (n=2),[56, 58] and physiotherapists and allied health assistants (n=1).[43] Volunteers delivered part or all of the intervention in four studies.[20, 41, 44, 52] Three studies did not report who delivered the intervention, including two single component interventions. [57, 60, 65] Most studies (n=25) wholly or partly tailored components and strategies to patients' individual needs (Table 3).

(Insert Table 3 Intervention characteristics here)

Abbreviations: ICU Intensive Care Unit, **NR** Not reported, **OA** On admission, **OT** Occupational therapist, **PT** physiotherapist **Component codes: C** Cognitive activity, **E** Physical activity, **H** Hearing, **V** Vision, **P** Sleep-wake cycle preservation, **W** Hydration, **S** Staff education, **F** Family involvement, **N** Nutrition, **Pa** Pain, **O** Oxygen, **L** Falls prevention, **G** Staff changes, **B** Bladder/bowel, **J** Environment/lighting/noise, **CA** Comprehensive assessment, **BT** Blood transfusion, **Z** Address medical complications, **PE** Patient education, **Ph** Physiological monitoring, **K** Pharmacological

Figure 5: Types and rates of intervention components, including for sample of interest
Code: P Delirium prevention studies, **P & T** Combined delirium prevention and treatment studies, **T** Delirium treatment studies, **S of I** Sample of interest

Adherence

Eighteen studies reported adherence to intervention strategies, using different methods and levels of detail (Supplementary Table 1). Almost all reported less than 100% adherence, with the exception reporting 100% geriatric nurse compliance with the "semi-structured protocol".[62] The palliative care unit study reported 89.7% overall adherence to the study protocol.[49] Three studies compared adherence to intervention strategies with that for control participants and reported that usual care sometimes mirrored some intervention strategies.[46, 50, 55] Two studies reported reasons for non-adherence: pharmacological sedation, coma and absence of a relative in the palliative care unit study; [49] and patient refusal or unavailability, staff member unavailability, and medical contraindications in the original HELP study.[20]

Study modifications

Two studies modified the intervention in the pilot phase, including changes in staff education and practice change materials,[39] and providing study information to family on admission rather than waiting until the researcher was present. [58] The palliative care unit study modified the primary outcome measure by not substituting the CRS for the CAM, due to CAM completion delays and poor completion rates (39% of participants) caused by "the challenge of conducting the baseline CAM structured interview in the last days or hours of life".[49]

Acceptability outcomes

Adverse effects

No study reported systematic processes of attribution of adverse effects to the intervention. Ten studies reported adverse events related to hospitalisation rather than the intervention [38, 44, 51-53, 55, 56, 62, 63] (Figure 4 and Supplementary Table 2). No study reported statistically significant increased adverse events for intervention participants. Two simply stated that the intervention had no adverse effects.[20, 43] A RCT,[55] a controlled trial [63] and a before-after study [62] reported statistically significant reductions in some adverse events for intervention participants: falls,[55] physical restraint,[62, 63] pressure ulcers,[55, 62] infection,[55, 62] and sleeping problems.[55]

Patient, family, clinician and volunteer subjective experiences

No study reported patients' subjective experiences of intervention (Supplementary Table 3). A survey of family caregiver's satisfaction with intervention and care for delirious patients within one study found most experienced moderate to high levels of distress (72%), believed that the environment and intervention helped the patient's recovery (86.6% and 83.5%, respectively) and that the three most useful strategies were activity, reality orientation and thrice-daily mobilisation.[62] A before-after study of older medical and surgical inpatients interviewed patients, volunteers, nurses and physicians and analysed meeting minutes to assess intervention integration in clinical practice, with minimal details of analysis methods and findings provided. [52] Four studies reported multidisciplinary and expert input during intervention development.[39, 40, 45, 61] The RCT of nocte earplugs in the ICU stated in the discussion that some participants preferred not to use them in order to remain "in direct contact with their environment". [47] No studies reported measures of patient distress related to delirium (Figure 5).

Discussion

This review found that studies of non-pharmacological delirium interventions frequently excluded and under-characterised people requiring palliative care and subsequently their outcomes were infrequently reported. The likely reasons for these findings and how to address barriers to inclusion and report characteristics and outcomes for this patient sub-group in future research are discussed.

With regards to inclusion, this review identified a selection bias against people requiring palliative care through exclusion of people expected to die (using various prognoses and terminology) and also of those with greater acuity or severity of illness, particular diagnoses and with cognitive, sensory and/or communication impairments. These exclusions were rarely explained or justified and often seemingly arbitrary. Nor were they consistent across the studies. These exclusions represented people highly at risk of delirium.[1, 6] This finding reflects those of other reviews that identified selection biases against people with dementia in geriatric research[76] and older people from clinical trials in oncology.[77] Reasons for the exclusions identified in our review are likely to be multifactorial. One factor may be assumptions that the interventions were not appropriate, possible or likely to be effective for people requiring palliative care, as indicated by the two studies which justified the exclusion of patients with a terminal condition and requiring comfort care as that the intervention would be unlikely to benefit them.[41, 44] Historical views that people requiring palliative care are separate from the wider hospital population, rather than universally and always within it, may also have influenced some exclusion decisions.[78, 79] There are also pragmatic challenges to ensuring informed consent and completion of study measures when patients are frail, expected to decline, and have pre-existing cognitive and sensory impairments. However, these challenges may be overcome through a variety of research strategies, such as proxy, opt out and advance consent methods, early contact, tailoring of interventions and messaging to patients and family, adequate research resources and governance, and cluster designs.[26, 27, 80, 81] Outcomes such as days alive without delirium or coma may promote the inclusion of more severely ill patients in future delirium research, because consciousness is pre-requisite for delirium measurement.[40, 82] Brief and

observational delirium diagnostic tools that can be validly used with patients with cognitive, sensory and communication impairment are also available.[83-86]

Despite most studies excluding certain groups of people likely to require palliative care, unsurprisingly we identified that they were indeed present, despite under-reporting of their characteristics and outcomes. One reason it was difficult to retrospectively distinguish this sub-group for the purposes of ascertaining their outcomes in this review was that the studies reported participants' diagnoses, illness severity, and mortality using different measures, time-points, methods and degrees of detail. While identifying inpatients with palliative care needs in hospital is challenging and an uncertain science, both retrospectively and prospectively, there are ways it can be achieved. [29, 87-89] In addition to the GSF PIG which we applied in this review, [29] the Palliative Care Needs Assessment Tool [90] and the Supportive and Palliative Care Indicators Tool (SPICT) [91] can be used to identify which patients are at risk of deteriorating and dying in hospital. Other studies suggest identifying patients with palliative care needs through the presence of life-threatening illness coupled with receipt and acceptance of care focused on supporting quality of life, [87] or retrospectively though the use of death registration data. [89] Such methods could be used in delirium intervention research in settings where mortality is high, such as intensive care units, where existing illness severity measures focus on acuity and intensity of intervention and, despite having some prognostic utility, were never designed to identify a patient's need for palliative care.[67, 74, 92]

Better characterisation of people requiring palliative care in studies of non-pharmacological interventions for delirium would help to build evidence of their outcomes in two ways.

Firstly, it would allow sub-group analysis to be performed and reported in future studies in any setting. This is important because the question of whether delirium can be prevented and treated through non-pharmacological means was not definitively determined for this population by this review. The multi-site palliative care unit study had the greatest number of participants and reported good overall adherence to the study protocol; [49] however, the only core care domain [21] was cognitive activity, consisting of nurses orientating patients to time, person and place each shift. Planned use of the CAM was not accomplished and the

substituted screening tool[93] was not a validated tool for delirium diagnosis or severity. All participants had 'terminal' cancer and died within 90 days of admission and thereby were not fully representative of people requiring inpatient palliative care, including in specialist units[49], not all of whom will die within three months. Only one geriatric unit study of people with dementia reported reduced delirium incidence; however, the report lacked detail, including of analysis methods.[57] The remaining three studies were focused on frail elderly patients with cancer, dementia, hip fracture and comorbidity following surgery,[42, 52, 53] a level of intervention and delirium risk that many people requiring palliative care would not undergo. Lastly, we found no studies focused on non-pharmacological interventions to treat delirium in people requiring palliative care, highlighting the particular need to research this challenging area of clinical care.

Secondly, better recognition of people requiring palliative care in delirium research would heighten awareness of their needs, which in turn would instigate consideration of outcomes that are most meaningful to them. Reducing delirium incidence, duration and severity, length of admission and mortality were the foci of the included studies. While worthwhile aims at any point in the illness trajectory, more person-centred outcomes, such as reduction of delirium related distress, and improved patient and family caregiver experiences of decision making, respect and dignity, and quality of life, were almost completely absent. [5, 94] Measuring these additional outcomes, which are highly valued by patients and family caregivers,[95, 96] would enrich this field of research and is achievable through both quantitative and qualitative methods. Adverse effects of intervention will also be important to systematically measure in future trials, given that patients with cognitive impairment have increased vulnerability to harm in hospital.[97]

Lastly, this review allowed an interpretation that many intervention components are feasible for people requiring palliative care by virtue of their delivery to elderly, frail and/or critically ill patients with and without delirium in the included studies. However, we suggest that studies measuring the feasibility of components of the original HELP intervention [20] that were subsequently found to be effective for other older hospitalised patients i.e. those targeting cognitive and physical activity, sleep, hearing, vision and hydration,[21-23] are necessary next steps within delirium research programs in specialist palliative care settings.

Limitations and strengths

A limitation of this review was that only English language studies were included. Another limitation was that our retrospective identification of people requiring palliative care was not sufficient to definitively determine outcomes for this patient sub-group; therefore this review makes only recommendations for future research, not clinical practice. A strength of this review was our systematic approach adhering to PRISMA.[30]

Conclusion

This review found that studies of non-pharmacological delirium interventions have excluded, poorly characterised and infrequently reported outcomes for people requiring palliative care. Based on these findings, we suggest new approaches to generate evidence for delirium interventions in this important patient sub-group. First, randomised controlled trials of non-pharmacological interventions to prevent and treat delirium are needed in specialist palliative care settings, with feasibility studies required before trials of effectiveness. Interventions should be based on those implemented and proven effective for older patients, especially those who were frail and severely ill with comorbidity. Second, broad inclusion criteria, justified exclusions, and tailoring in future inpatient trials of non-pharmacological delirium interventions would promote representative study populations. Third, systematic characterisation of the sub-groups of people requiring palliative care would allow their specific outcomes to be reported. Last, additional outcomes related to patient and family subjective experience, goals of care and quality of life would enhance the relevance of delirium research in inpatient settings where people are cared for at the end of life.

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Table 1 Study characteristics

Author, year	Country	Aim	Design	Service/setting	Component	Risk of bias Δ
Moon 2015 [61]	Korea	P	RCT	105-bed medical/surgical ICU, general 1049-bed hospital	M	2,6,7,9,10
Bakker 2014 [52]	Netherlands	P	BA	Frailty service, two surgical + one internal medicine department, university MC	M	6,7,9,10
Bryczkowski 2014 [38]	US	P, T	BA	14-bed surgical ICU, Level I academic urban trauma centre	M	6,10
Chong 2014 [62]	Singapore	T	BA + Control	Geriatric Monitoring Unit for acute delirium	M	6,7,10
Patel 2014 [64]	UK	P	BA	24-bed adult mixed surgical/medical ICU, teaching hospital	M	6,7,10
Gruber-Baldini 2013 [65]	US & Canada	P, T	RCT	Postoperative hip fracture services in thirteen hospitals	S	2,3,6,7,9,10
Hempenius 2013 [53]	Netherlands	P	RCT	Solid tumour perioperative services at university MC, large teaching hospital + community hospital	M	2,3,5,6,7,10
Holt 2013 [39]	US	P	BA	Three specialist elderly care wards, general hospital	M	6,7,9,10
Jeffs 2013 [43]	Australia	P	RCT	Medical inpatients, secondary referral hospital	M	2,3,4,5,6,7,8,10
Kamdar 2013 [40]	US	P	BA	Medical ICU, tertiary academic hospital	M	1,6,9,10
Zaubler 2013 [41]	US	P	BA	38-bed general medical floor, 600-bed teaching community hospital	M	7,10
Andro, 2012 [57]	France	P	BA	Acute geriatric care unit	M	6,10
Deschodt 2012 [46]	Belgium	P	CT	Perioperative hip fracture in two trauma wards, university hospital	M	6,8,9,10
Gagnon 2012 [49]	Canada	P	QE	Four hospital palliative care units + three stand-alone hospices	M	7,9
Martinez 2012 [56]	Chile	P	RCT	Internal medicine ward in an acute hospital	M	1,2,3,6,7,8,10
Van Rompaey 2012 [47]	Belgium	P	RCT	45-bed medical/surgical/cardiac surgical ICU, 625-bed university hospital	S	2,3,5,6,9
Black 2011 [58]	Ireland	P	CTS	Seven-bed medical and surgical ICU, inner city public hospital	M	9
Bo 2009 [59]	Italy	P	CT	Medical and geriatric units, university teaching hospital	M	6,7,9
Vidan 2009 [63]	Spain	P	CT	Geriatric and internal medicine units, large public university hospital	M	6,7,8,9,10
Caplan & Harper 2007 [44]	Australia	P	BA	52 bed geriatric ward, tertiary referral university hospital	M	6,7
Lundström 2007 [55]	Sweden	P, T	RCT	Postoperative hip fracture service in geriatric orthopaedic + orthopaedic ward, university hospital	M	2,3,5,6,7,8,9,10
Taguchi 2007 [60]	Japan	P	PRCT	Postoperative oesophageal cancer service, university hospital	S	3,6,10

Author, year	Country	Aim	Design	Service/setting	Component	Risk of bias [Δ]
Lundström 2005 [54]	Sweden	P, T	CCT	Two hospital wards, general internal medicine department	M	1,5,6,9
Wong 2005 [45]	Australia	P	BA	Hip-fracture service in orthopaedic ward, 460-bed metropolitan teaching hospital	M	1
Cole 2002 [50]	Canada	T	RCT	Five medical units, 400-bed university-affiliated primary acute care facility	M	2,3,5,6,7,8,9,10
Marcantonio 2001 [42]	US	P, T	RCT	Perioperative hip fracture service, academic tertiary MC	M	2,3,5,6,7,8,9,10
Milisen 2001 [48]	Belgium	P, T	BA	Perioperative hip fracture service, emergency room + two trauma units, urban academic MC centre	M	6,10
Inouye 1999 [20]	US	P	CT, matched	200 bed general-medicine service, 800-bed urban teaching hospital	M	6,8,9,10
Cole 1994 [51]	Canada	T	RCT	Medical inpatients of university-affiliated, primary acute 400-bed hospital	M	1,5,6,8,9,10

Code: P Prevention, **T** Treatment, **RCT** Randomised controlled trial, **CTS** Comparative time series, **B/A** Before–after study, **CT** Controlled trial, **ICU** Intensive Care Unit, **NR** Not reported, **MC** Medical Centre, **M** Multicomponent, **PRCT** Pilot RCT, **QE** Quasi-experimental, **S** Single component

[Δ] Numbers signify the domains in which the study was assessed as having **low risk of bias**: 1 = Representative study sample; 2 = Concealed allocation; 3 = Random sequence generation; 4 = Blinded participants and intervention personnel; 5 = Blinded outcome assessors; 6 = Valid, reliable delirium measures; 7 = <20% sample lost to analysis; 8 = Intention to treat analysis; 9 = Confounders accounted for; 10 = Only *a priori* outcomes reported

Table 2 Study inclusion and exclusion criteria and participant diagnoses, illness severity and mortality

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
Moon 2015[61]	≥ 18, ability to understand study purpose and/or provide consent independently or via proxy, ICU admission ≥48 hours	Persistent RASS - 4 or -5, severe visual and auditory problems preventing CAM-ICU, serious psychiatric or neurologic diagnosis, Korean MMSE score ≤23, † on isolation ward with infection; death or discharge day admitted, inability for CAM-ICU when patient violent with RASS +3 or +4	134	69.7	48	Infection 25	APACHE II 13.9	7-day in-hospital 1 (1.7%) vs 9 (14.3%)*† 30-day in-hospital 4 (6.7%) vs 11 (17.5%) †
Bakker 2014[52]	≥70, admitted to surgical or medical departments > 48 hrs, at risk of delirium, falls, malnutrition, physical decline, frail†	Illness, language barriers, other speciality, refusal, logistic missing, delirium O/A, refusal, died in hospital,† died <3 months†	386	77	56	NR	ASA: I and II 25.5% III and IV 74.5%† CIRS-G comorbidity 13	During admission 5 (3%) vs 3 (2%) † Three-month 8 (4%) vs 11 (6%) †
Bryczkowski 2014[38]	>50, admitted to SICU ≥ 24 hours	Moderate-severe traumatic brain injury (AIS score 3) †, transfer from jail or in police custody, h/o dementia.† Participants with unobtainable or undocumented	123	66.5	58	NR	GCS 14.6 ISS 16.5 (Trauma patients)	In-SICU 2 (3%) vs 4 (7%) ††

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
		delirium status excluded from analysis						
Chong 2014[62]	> 65, admitted to geriatric medicine department, assessed to have delirium (either O/A or incident delirium during hospital stay) according to CAM	Medical illness needing special monitoring, dangerously ill† coma, terminal illness,† uncommunicative or severe aphasia, † severe combative behaviour with high risk of harm, contra-indication to bright light therapy, respiratory or contact precautions, GMU admission refused by family, patient or physician-in-charge	320	84.3	33	NR	CCI 2.7 † Severity of Illness Index: Level 1 0.9% Level 2 84.3% Level 3 14.8% †	During admission 4 (1.7%) vs 0 † 6-month 20 (12%) † 12-month 14 (20.5%) (Intervention cohort only) †
Patel 2014[64]	> 18, ≥1 night in ICU	Pre-existing sleep pathology, severe visual or hearing impairment, alcohol addiction or illicit drug abuse, h/o CI, † discharge from ICU this admission, neurosurgical, delirium during study, received	338	60.3	52	NR	APACHE II 14.6	NR

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
		sedative medications within 24 hrs						
Gruber-Baldini 2013[65]	≥ 50, surgical repair of hip fracture, haemoglobin <10 g/dL <3 days after surgery, CVD or CVD risk factors	Unable to walk without human assistance prior to hip fracture, declined blood transfusion, multiple trauma, † pathologic hip fracture,† acute MI <30 days prior to randomisation, prior enrolment, symptoms of anaemia, actively bleeding at time of potential randomisation, non-English speaking	139	81.5	26	Hip fracture & CVD/CVD risk factors 100 **Comorbid:** Dementia 32††/AF 32/Chronic lung disease 21/DM 20/ Hearing problems 18/Visual problems 12/Stroke/TIA 12/ Ca 11/Alcohol abuse or withdrawal 11/Parkinson's 3†	ASA 2.9	NR
Hempenius 2013[53]	>65, undergoing elective surgery for solid tumour, frail according to >3 on Groningen Frailty Indicator† at outpatient departments at participating centres	Unable to fill in questionnaire, unable to complete the study protocol and follow-up schedule before inclusion (e.g. logistical reasons or if extra hospital visits too burdensome)	297	77.5	36	>2 comorbidities 60 (diabetes, COPD, HT, MI, other CVD, hearing and vision problems, memory problems, neurological, cerebrovascular, psychiatric or musculoskeletal disorders)/ RF 3†	**Surgery** Minor 25.9% Intermediate 21.9% Major 52.2%	In-hospital 7.9% vs 3% (n=14 overall) †
Holt 2013[39]	Admitted with acute medical illness from ED directly by GP to	Prevalent delirium, too unwell to be assessed (in opinion of clinical staff),†	362	85.4	42	CI (<24 MMSE) 58/Hearing impairment 59 Visual impairment 31	CCI ≥ 4 19.8† Severe illness (>3	In-hospital 17 (11.2%) vs 23 (11.0%) †

Author, year	Inclusion	Exclusion	Sample size [Δ]	Age, Mean [Δ]	Male % [Δ α]	Diagnoses % [Δ α]	Illness severity, mean or proportion [Δ]	Mortality I vs C n (%)
	participating geriatric wards	unable to communicate verbally in English, consent not obtained <24 hours O/A					MEWS) 0.4% [†]	Six-month post-discharge 50 (33.8%) vs 64 (30.9%) [†]
Jeffs 2013[43]	≥ 65, admitted to medical unit in the study area, in hospital <48 hours	Severe dysphasia making communication impossible, death expected <24 hrs,[†] infection control isolation, contraindication to mobilisation, admission to Stroke Unit or critical care, planned admission <48 hours, major psychiatric diagnosis, prior enrolment, delirium documented O/A, transfer from other hospital	647	79.4	48	Visually impaired 23 Hearing impaired 20 Premorbid CI 14	APACHE II 14.1 CCI median, IQR) 2 (1–3)[†]	NR
Kamdar 2013[40]	≥ 70, admitted from ED to participating medical ICU	None	300	54	52	Respiratory failure 30[†]/GI 15/ Sepsis (non-pulmonary) 12[†]/CVD 11/Other 32	NR for whole cohort	ICU 24 (14%) vs 18 (16%) [†] In-hospital 34 (19%) vs 28 (25%) [†]
Zaubler 2013[41]	≥70, admitted to general medical floor	Not likely to benefit from the interventions i.e. non-verbal, terminal illness and receiving comfort care,[†] refusal	595	82.7	43	CI 91/ Pneumonia 8/UTI 7 Malaise/fatigue 6/ Cellulitis 5/Other 70	NR	NR

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
Andro 2012[57]	≥75 years, admitted to acute geriatric unit, demented, † not delirious	None	255	84.8	31	Dementia 100†	NR	NR
Deschodt 2012[46]	≥65, verbally testable, admitted to ED with a traumatic hip fracture	No traumatology admission, poly-trauma, premorbid assessment missed, life expectancy < 6 months,† refusal, pathological fracture, no surgery, non-native speaker, no admission via ED, hard of hearing	171	80.8	27	Hip fracture 100 Dementia 21†	CCI 2.3	One-year 10 (33%) vs 13 (22%) †
Gagnon 2012[49]	Admitted to participating palliative care units and hospices†	Delirious on admission or within 48 hours of admission, hospitalised < 48 hours and > 90 days, alive at discharge	1516	68.4	46	Terminal cancer 100† **Comorbid:** Depression 5/Anxiety 1.3/ Bipolar 0.5/Alzheimer's 0.5/ Other dementias 0.8/ Schizophrenia or psychosis 0.6/ Alcoholism 0.5/ Drug dependence 0.05/ Personality disorders 0.2/ Other psychiatric 0.7	NR	90-days 1516 (100%) (all) †
Martinez 2012[56]	All internal medicine ward patients at risk of delirium i.e. presence of at least one risk	Delirium O/A, no family support, refused consent, admitted to a ward other than general internal medicine, in	287	78.2	63	HF 29/ COPD 22/ Ca 18/ CKD 14/Acute MI 9/ Mild CI 8/ DM with end-organ damage 8/ Dementia† 6 /PVD 6/Previous delirium	CCI median (IQR) 2 (1–4 †	NR

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
	factor: >70, previous history of CI, † MMSE score <24 prior to admission, alcoholism, metabolic imbalances O/A	a room with > two beds				4/Mild liver disease 4/ Mesenchymopathies 4/Peptic ulcer disease 3/Metastatic Ca 3† /Severe liver disease 2† /Lymphoma 0.7 /Leukaemia 0.4		
Van Rompaey 2012[47]	≥18, expected LOS in ICU >24 hours, Dutch or English speaking, GCS score ≥10	Hearing impairment, dementia†, confusion or delirium O/A	136	59.5	66	≥ 1 Comorbidity 72 †	SOFA score first 24 hrs 7.1 SAPS 3 2.3 Maximal RIFLE: No acute kidney injury 6.3% Risk 6.2% Injury 17.9% Failure 69.6% †	During study period 2 (1%) (overall) †
Black 2011[58]	≥18 years, admitted to medical and surgical ICU, family member willing to participate	Terminal diagnosis†	170	>60 73%	NR	NR	NR	12-week 32 (19%) (overall) †
Bo 2009[59]	≥ 70 years, admitted from ED to participating medical and geriatric units	Delirium during ED stay or O/A, history of primary psychiatric disorder or alcohol abuse, coma, † aphasia, † intubation,	252	82.5	48	NR	APACHE II 14.3 CIRS comorbidity index 4.1†	NR

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
		or stroke OA, † language barrier, absence of a caregiver					CIRS Severity index 0.4	
Vidan 2009[63]	≥70, not delirious O/A, at least one of four delirium risk factors (CI, † visual impairment, acute disease severity, † dehydration), admitted to participating geriatric and internal medicine units	Severe dementia with impaired communication,† aphasia, coma, agonic status, expected hospital stay ≤ 48 hours	542	84	43	**Comorbid:** mean 2.7 **Primary O/A:** Visual impairment 60/Hearing impairment 55/Infection 43/HF 21†	APACHE II 11.3	In-hospital 10 (5.8%) vs 19 (5.1%) †
Caplan and Harper 2007[44]	≥70, able to communicate and enrolled O/A to geriatric wards, presence of at least one risk factor for delirium (MMSE < 24, sleep deprivation, ADL, vision or hearing impairment, immobility, dehydration)	Patients who would not receive a benefit (severe dementia (MMSE < 10), psychotic disorder, unable to consent or refusal, terminal condition and receiving comfort care,† expected discharge <48 hours) or behavioural or medical condition that may risk volunteers' health and safety	37	84.7	22	Fracture 36/ Infection 32/ Collapse 13	NR	NR vs 1 (5%)

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
Lundström 2007[55]	≥70 years, consecutively admitted to orthopaedic department with femoral neck fracture	<70, severe RA, severe hip osteoarthritis; severe RF†, pathological fracture,† bedridden before fracture†	199	82.2	26	**Comorbid:** CVD 57/ OP 52/ HT 43/ Impaired hearing 43/Depression 40/Impaired vision 39/Dementia 32†/Stroke 25/DM 20/Wrist fracture 20/Lung diseases 16/ Hip fracture 15	GDS-15 4.9	In-hospital 6 (3%) vs 7 (7%) † Four-month 3 (3%) vs 6 (7%) † 12-month 7 (8%) vs 5 (7%) †
Taguchi 2007[60]	Oesophageal Ca surgery, capable of communicating in Japanese	Mental or ophthalmologic disorders, reintubation, medical complications, deterioration of condition†	15	57.5	100	Oesphageal Ca 100/ Diabetes 20/HT 9	NR	NR
Lundström 2005[54]	≥ 70, consecutively admitted to participating medical wards	<70, refusal to participate	400	80.1	44	**Comorbid:** DM 33/Stroke 25/Asthma12/ Ca 1/Dementia 4.5† /Epilepsy 4.5 **O/A:** HF 25/Infection 18/Impaired vision 16/Stroke 11/MI 7/Epilepsy 6/Fever ≥38C 6/UTI 5/Impaired hearing 3	NR	In-hospital (delirious patients) 2 (3.2%) vs 9 (14.5%)*†
Wong 2005[45]	> 50, osteoporotic hip fracture, admitted to orthopaedic ward during study period	None	99	81.8	26	Operation <24 hrs O/A 78/Vascular disease 41/Chronic lung disease 18/Diabetes 14/Renal impairment 11/Depression or anxiety 6	NR	3-month study period 3 (4.2%) vs Baseline 28-days 2 (7.1%) †

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
Cole 2002[50]	≥65, admitted to participating medical units with delirium O/A or < 1 week of admission	Primary diagnosis of stroke, † ≥48 hour stay on ICU or cardiac monitoring unit, geriatric or oncology service admission, unable to speak English or French, residence outside Montreal	227	82.4	46	Dementia 58†	CCI 3.3 CSI 5.8	8-week 25 22.1%) vs 22 (19.3%) †
Marcantonio 2001[42]	≥ 65, admitted to the participating centre for primary surgical repair of hip fracture	Metastatic ca or other comorbid illnesses likely to reduce life expectancy <6 months†, unable to obtain informed consent <24 hours of surgery or 48 hours of admission	126	79	22	Hip fracture 100/Pre-fracture dementia 44†	≥4 CCI 36% ≥4 BDRS score 44%	NR
Milisen 2001[48]	Admitted to ED with traumatic fracture of proximal femur, hospitalized in one of the two trauma units <24 hours of surgery, Dutch-speaking, verbally testable	Multiple trauma, † brain concussion, pathological fractures,† surgery >72 hours after admission, aphasia,† blindness, deafness, <9 years of formal education	120	81 (median)	19	**Comorbid:** Previous operations 58/Cardiac 22/HT 18/ Vision or hearing problems 16/ DM 15/Dementia 15† /Vascular 15/Pulmonary 13/Abdominal 13/Depression 11/Urinary 8/ Associated fracture 3/Other 24	NR	NR

Author, year	Inclusion	Exclusion	Sample size Δ	Age, Mean Δ	Male % Δ α	Diagnoses % Δ α	Illness severity, mean or proportion Δ	Mortality I vs C n (%)
Inouye 1999 [20]	≥ 70, admitted to one of three general-medicine units, no delirium O/A, baseline intermediate or high risk for delirium	Unable to participate in interviews (profound dementia precluding verbal communication,† language barrier, profound aphasia, † intubation or respiratory isolation), coma or terminal illness,† hospital stay ≤ 48 hrs, prior enrolment, other (e.g., interviewer or patient unavailable)	852	79.7	39	**Primary:** Pneumonia 12/Chronic lung disease 12/CHF 11††/IHD 8/GI 13/DM or metabolic disorder 5/Ca 3/CVD 3/RF† 3/Anaemia 2/Other 32	APACHE II 15.6 BDRS 0.5 >2 Score 11.5%	In-hospital 6 (1.4%) vs 7 (1.6%) †
Cole 1994 [51]	≥75, delirious first 24 hrs OA to medical department, English or French speaking, not admitted to ICU or cardiac monitoring unit or referred to oncology or geriatric services, delirious	Primary diagnosis of CVA,† not delirious	88	86.1	54	Dementia 56 † (intervention cohort)	NR	8-week 14 (33%) vs 17 (37%) †

* Statistically significant difference Δ Intervention and control participants combined α Rounded to nearest whole number † Interpreted as indicating need for palliative care

Illness severity measures: Higher scores represent higher illness severity. **AIS** Abbreviated Injury Scale, **APACHE II** Acute Physiology and Chronic Health Evaluation (scores 0-71), **ASA** American Society of Anesthesiologists physical status classification (I: normal healthy patient - VI: a declared brain-dead patient

whose organs are being removed for donor purposes), **BDRS** Blessed Dementia Rating (scores 0-28, cut-off for impairment > 4), **CCI** Charlson Comorbidity Index (scores 0-37), **CIRS-G** Cumulative Illness Rating Scale–Geriatrics (scores 0-56), **CSI** Clinical severity of illness (1 (mild) - 9 (moribund)), **GCS** Glasgow Coma Scale (scores 3-15; scores 3-8 = coma), **GDS-15** 15-item Geriatric Depression Scale (≥6 = suggests depression and need for assessment, ≥11 = depression/severe depression), **ISS** Injury Severity Score (scores 1-75), **MEWS** Modified Early Warning Score (score ≥5 is statistically linked to increased likelihood of death or admission to an intensive care unit), **RIFLE** (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease categories), **SAPS 3** Simplified acute physiology score **(scores** 0-217), **SOFA** Sepsis-related Organ Failure Assessment (scores 0 to 24). **Other abbreviations: ADL** activities of daily living, **AF** atrial fibrillation, **Ca** cancer, **CAM** Confusion Assessment Method, **CAM-ICU** Confusion Assessment Method for the Intensive Care Unit, **CI** cognitive impairment, **CKD** Chronic Kidney Disease, **COPD** chronic obstructive pulmonary disease, **CVD** cardiovascular disease, **CVA** cerebrovascular accident, **DM** diabetes mellitus, **ED** Emergency Department, **GI** gastrointestinal, **HF** heart failure, **hrs** hours, **HT** hypertension, **I/C** intervention/control**, ICU** intensive care unit, **IHD** ischaemic heart disease**, IQR** interquartile range, **MI** Myocardial Infarction, **MMSE** Mini-Mental State Examination, **NR** not reported, **O/A** on admission, **OP** osteoporosis, **PVD** peripheral vascular disease, **RASS** Richard Agitation Sedation Scale, **RF** renal failure, **SD** standard deviation, **SICU** surgical intensive care unit, **TIA** transient ischemic attack, **UTI** urinary tract infection.

Table 3 Intervention characteristics

Author, year	Care components	Tailored	Who delivered
Moon 2015 [61]	C, H, P, V, W, S, F, N, Pa, O, B, J, K, CA, Z	✓	Four researchers, ICU nurses
Bakker 2014 [52]	C, E, S, N, L, K, CA	✓	Nurses, physicians, trained volunteers, with training delivered by geriatric team
Bryczkowski 2014 [38]	P, S, F, D, J, K, PE	✓	Whole team, research staff, family
Chong 2014 [62]	C, E, H, V, P, W, G, J	NR	Trained geriatric nurses, cognitive assessment by consultant geriatrician O/A
Patel 2014 [64]	C, E, P, S, D, Pa, J, K	✓	Physicians, nurses, PT, senior staff acting as champions
Gruber-Baldini 2013 [65]	T (blood transfusion)	✓	NR
Hempenius 2013 [53]	C, E, H, V, N, CA	✓	Consultant geriatricians and geriatric nurses
Holt 2013 [39]	C, E, H, V, S, Pa, B	NR	Specialist nurse, consultant geriatrician, nurse manager, ward staff
Jeffs 2013 [43]	C, E	✓	Allied health assistant, PT
Kamdar 2013 [40]	P, S, J, K	✓	Bedside staff
Zaubler 2013 [41]	C, H, V, P, W, S, N, K	✓	Elder Life Specialists, volunteers
Andro, 2012 [57]	C, J	NR	NR
Deschodt 2012 [46]	G, CA	✓	Consultative geriatrician, nurse, social worker, occupational therapist, physiotherapist, bedside staff
Gagnon 2012 [49]	C, F, K	✓	Bedside and research nurses, physicians
Martinez 2012 [56]	C, H, V, F	✓	Family members with education by researchers
Van Rompaey 2012 [47]	P (earplugs)	✗	Nurses
Black 2011 [58]	F	✓	Nurses, family
Bo 2009 [59]	C, E, P, W, S, F, N, Pa, K	✓	Physicians, nurses, PT
Vidan 2009 [63]	C, E, H, V, P, V, W, S, N	✓	Geriatricians, residents, nurses (including a full-time specialist geriatric nurse)
Caplan & Harper 2007 [44]	C, H, V, W, N	✓	Volunteers, volunteer coordinator
Lundström 2007 [55]	E, P, W, S, N, Pa, O, L, G, B, K, CA, Z, Ph	✓	Nurses, PT, OT, dietician, geriatricians; liaison with orthopaedic surgeons, geriatricians and community colleagues for post-hospital care
Taguchi 2007 [60]	J (bright light)	✓	NR
Lundström 2005 [54]	S, F, G	✓	All ward staff
Wong 2005 [45]	C, E, H, V, P, W, F, N, D, Pa, O, B, J, Z, K	✓	Geriatric registrar, geriatric team, nurses, nursing assistants, anaesthetist, pharmacist
Cole 2002 [50]	C, E, H, V, F, G, J, CA	✓	Geriatric internist, geriatric psychiatrist, study nurse, bedside nurses

Author, year	Care components	Tailored	Who delivered
Marcantonio 2001 [42]	C, E, H, V, W, N, D, Pa, O, G, B, J, CA, Z, K	✓	Geriatrician consulting to orthopaedics team
Milisen 2001 [48]	S, Pa, G, K	NR	Nurses
Inouye 1999 [20]	C, E, H, V, P, W	✓	A geriatric nurse, therapeutic-recreation and two Elder Life Specialists, PT, geriatrician, volunteers
Cole 1994 [51]	C, E, H, V, F, J, CA	✓	Geriatrician, geriatric psychiatrist, liaison nurse

Abbreviations: ICU Intensive Care Unit, **NR** Not reported, **OA** On admission, **OT** Occupational therapist, **PT** physiotherapist **Component codes: C** Cognitive activity, **E** Physical activity, **H** Hearing, **V** Vision, **P** Sleep-wake cycle preservation, **W** Hydration, **S** Staff education, **F** Family involvement, **N** Nutrition, **Pa** Pain, **O** Oxygen, **L** Falls prevention, **G** Staff changes, **B** Bladder/bowel, **J** Environment/lighting/noise, **CA** Comprehensive assessment, **BT** Blood transfusion, **Z** Address medical complications, **PE** Patient education, **Ph** Physiological monitoring, **K** Pharmacological

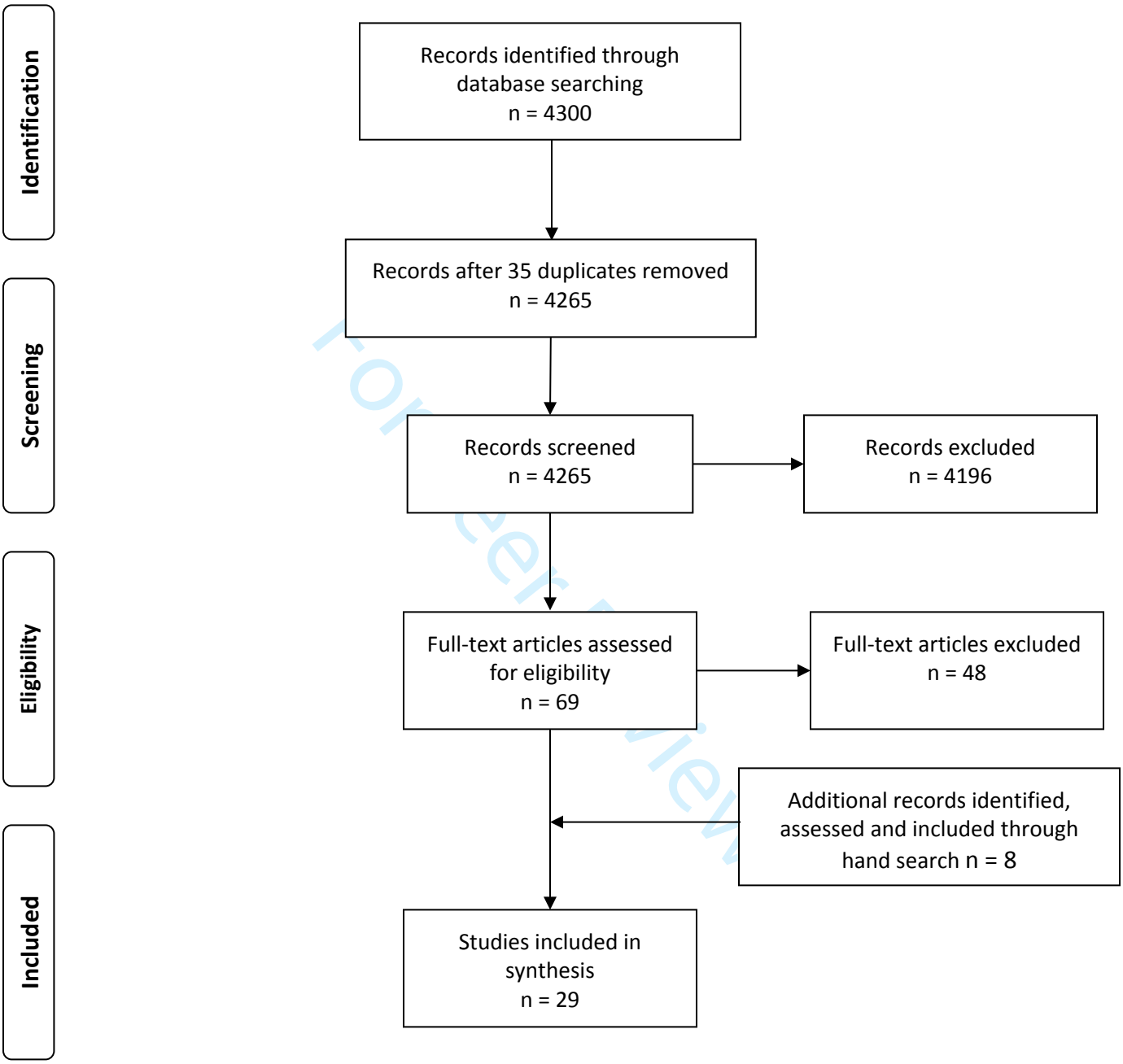

Figure 1 PRISMA Flow Diagram

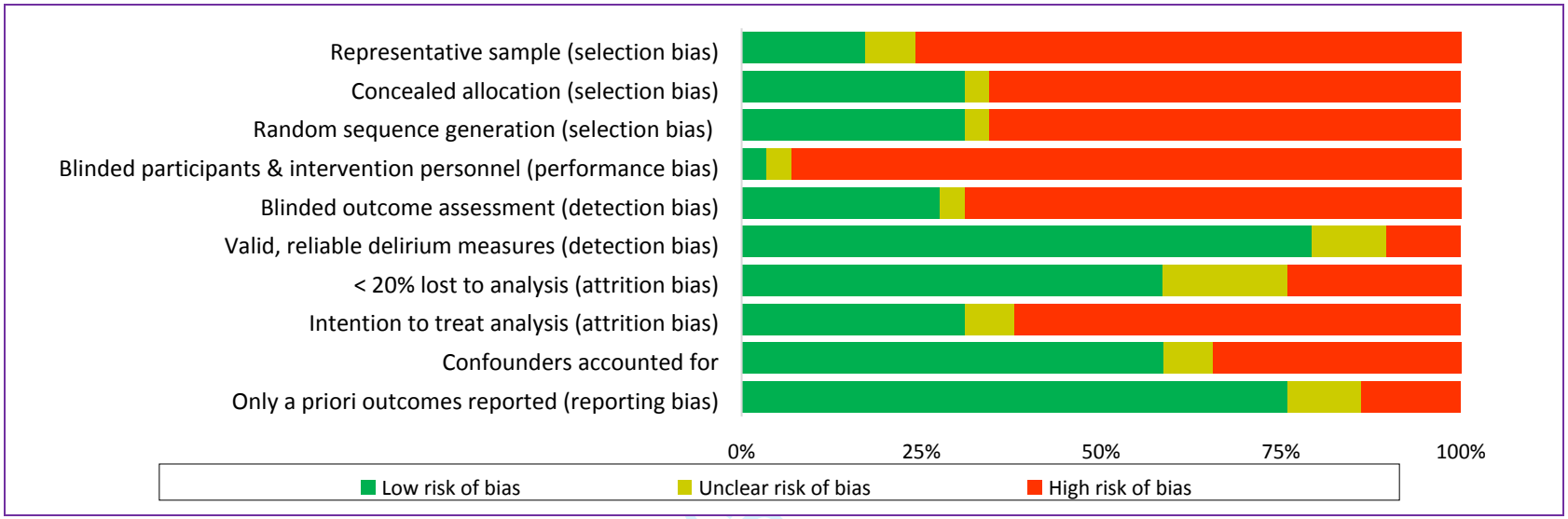

Figure 2 Overall risk of bias

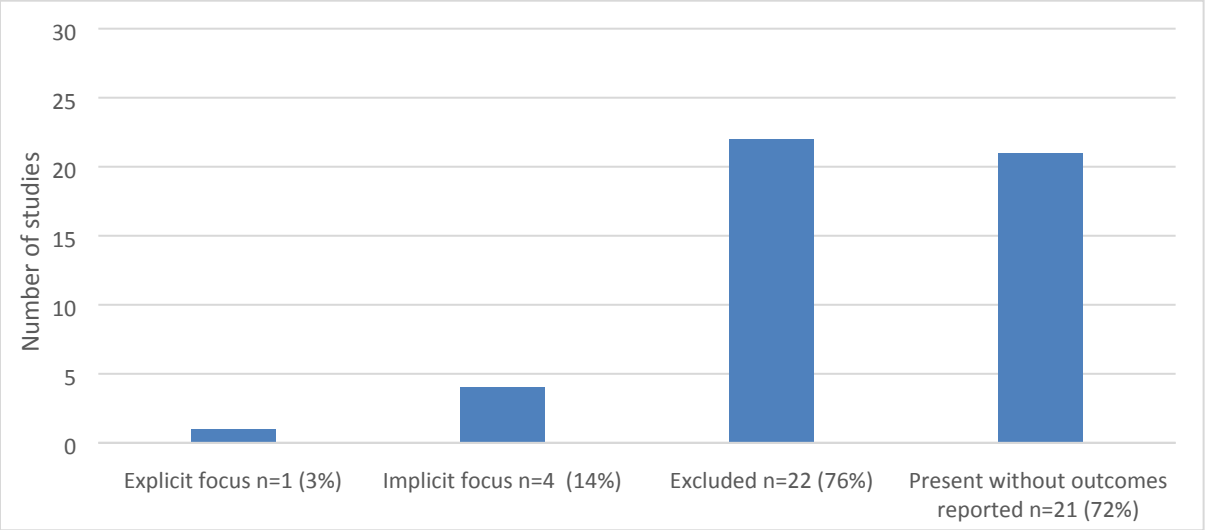

Figure 3 Study approaches to people requiring palliative care
NB: Combined percentages do not add up to 100% as studies simultaneously excluded and reported people requiring palliative care.

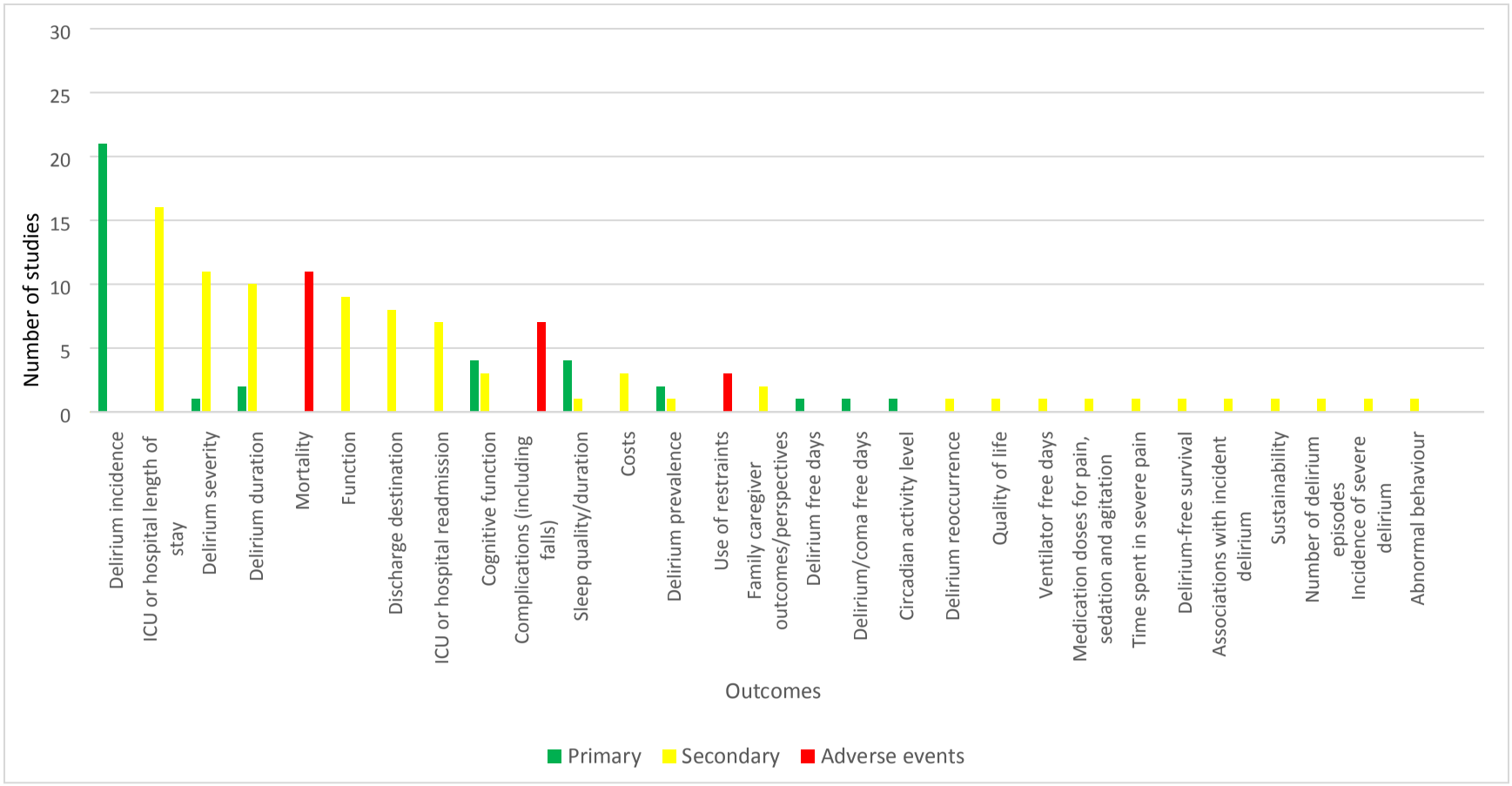

Figure 4 Types and rates of outcomes

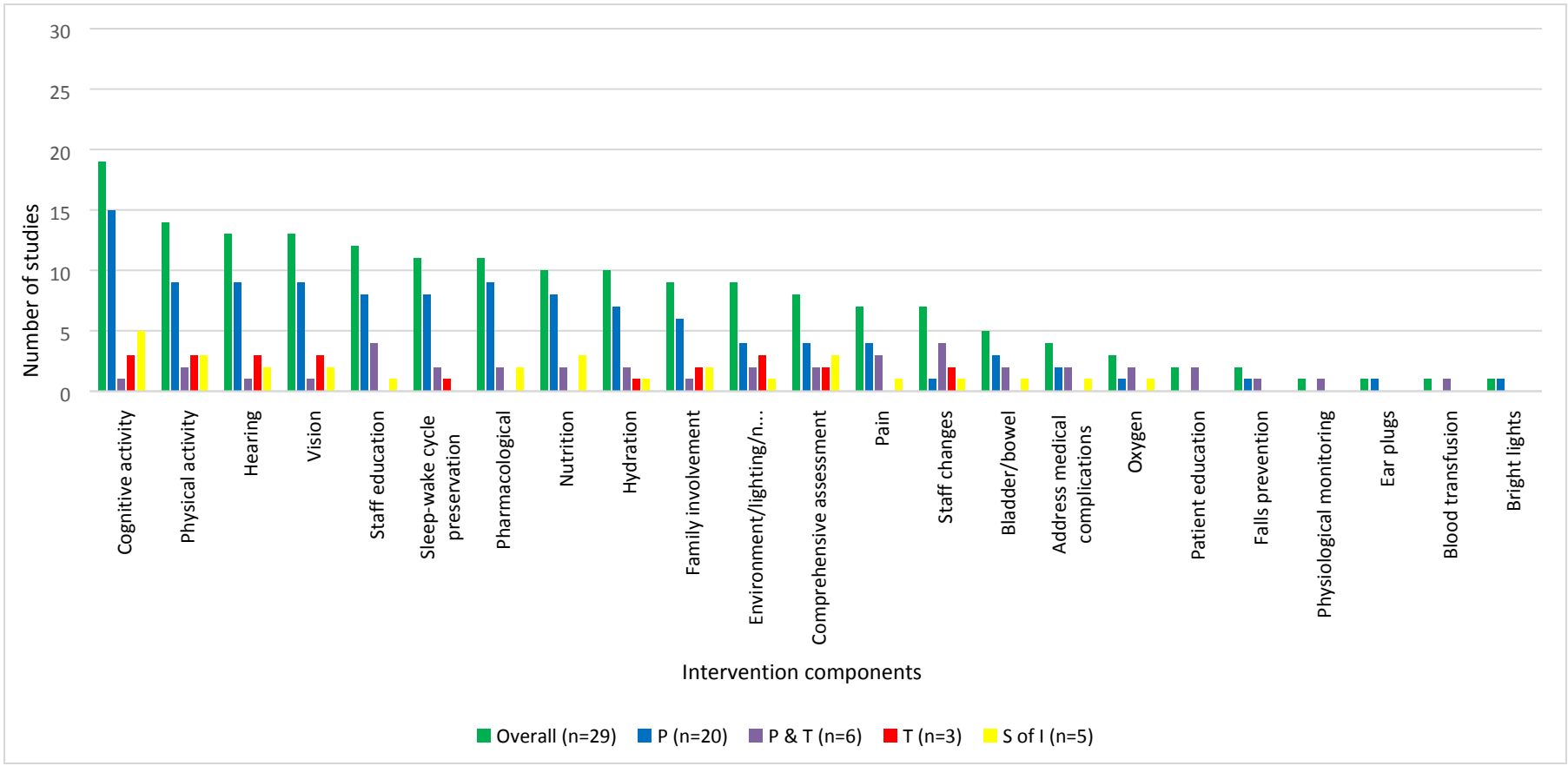

Figure 5 Types and rates of intervention components, including for sample of interest

Code: P Delirium prevention studies, **P & T** Combined delirium prevention and treatment studies, **T** Delirium treatment studies, **S of I** Sample of interest

Author, year	Adherence	Modifications
Moon 2015 [1]	NR	NR
Bakker 2014 [2]	**[Bold:** indicated and delivered by Carewell team; not bold: indicated and delivered by departments. Ranges are % of patients for whom adherence confirmed (lower value) to % of patients for whom adherence likely but not confirmed (upper value)]. Frail patients **100%,** CareWell plan **95%,** Medication review **94%** 91%, Therapeutic activities **92%,** Volunteers **84%** 46% (46% represents mean % of visits performed of the total which could be performed (data from 49 patients), Information in discharge letter **74%** 55%, Orientation points **71%** 83–92%, Orientation **60%**, Consult physiotherapist **59%** 56–68%, Nutrition **53%,** Day program activities **50%** 52–57%, Day program delirium **48%** 46–59%, CGA by geriatrician **42%** NA, Registration food intake **40%** 74–83%, Medical history by proxy **32%**, Consult dietitian **33%** 37–40%, Falls sensor **22%** 46–48%, Discharge planning **16%** 100%, NA, Mobilizing **15%**, Multidisciplinary meeting **11%** NA.	NR
Bryczkowski 2014 [3]	NR	NR
Chong 2014 [4]	100% compliance to semi-structured protocol by trained geriatric nurses	NR
Patel 2014 [5]	Overall compliance with interventions > 90%. **Noise:** Offer earplugs to all patients with RASS > 4 100%, Staff and visitors to speak quietly 96%, Close all doors 96%, Turn monitoring equipment to night mode 23:00-07:00 96%, Reduce volumes on all telephones 23:00-07:00 96%, No non-clinical discussions around patients' bed spaces 92%; **Light:** Dim main ICU lights 23:00-07:00 100%, Use bedside lighting for patient care 26 100%, Offer eye-masks to all patients with RASS > 4 25 96%; **Patient care:** Orientate patients regarding time, place and date every eight hours 100%, All patients requiring mechanical ventilation of the lungs to be assessed daily for suitability for sedation hold or trials of spontaneous breathing 100%, Hourly pain scores and prompt action to optimize analgesia 100%, Set appropriate sedation targets once per day (based on RASS) 100%, If patients sleep poorly or have a positive result on the CAM-ICU, perform a medication review within 24 h 96%, Complete care procedures before 23:00 or delay completion until after 08:00 where possible 92%, Group care/procedures where possible 88%, Ensure early mobilization when possible and appropriate 88%.	NR
Gruber-Baldini 2013 [6]	Number of units of blood transfused: None 4.5%, One unit 40.9%, Two units 36.4%, Three units 12.1%, ≥ four units 6.1%. Total units of blood transfused post-randomization = 115 in 66 participants.	NR
Hempenius 2013 [7]	NR	NR
Holt 2013 [8]	Staff attendance at delirium education sessions 70%, Adherence to delirium risk factor modification protocols 27–57%. Protocol adherence highest for reorientation and hydration, lowest for mobility and constipation	During pilot phase, materials for education and practice change (30-min interactive lecture with a handout, a delirium quiz, a poster, reference material and case vignettes) were modified following consultation with local opinion leaders.
Jeffs 2013 [9]	Therapeutic encounters per day, median 1.4 (0.9–1.8), minutes of therapy per day median 38 (25– 52)	NR

Kamdar 2013 [10]	Checklist item completion rates 86-94%. **Patient daytime interventions:** Blinds raised 79%, Caffeine avoided after 3pm 54%, Less than 50% of day shift spent napping 45%. **Patient nighttime interventions:** Room lights dimmed before 10pm 78%, Unnecessary alarms prevented 77%, Room temperature optimized 77%, Pain appropriately controlled 68%, Room curtain closed before 10pm 64%, Warm bath before 10pm 49%, Television off 59%, Medication given per sleep guideline 13%, Soft music offered and accepted 11%, Eye mask offered and accepted 2%, Earplugs offered and accepted 1%. **ICU-wide nighttime interventions:** Hallway lights dimmed by 10pm 89%, Overhead pages after 10pm: none 15%, 1-3 36%, >3 8%, unknown 41%. **Estimated number of nurse interruptions between 10pm-7am:** 0-5 interruptions 28%, 6-10 interruptions 21%, >10 interruptions 13%, NR 37%.	NR
Zaubler 2013 [11]	NR	NR
Andro, 2012 [12]	NR	NR
Deschodt 2012 [13]	No significant differences between groups in care given except intervention participants received more occupational therapy (intervention 69.1%, control 41.6%, $p < 0.001$) and opioid pain medication (intervention 91.5%, control 75.3%, $p=0.004$) than controls. **2011 primary report:** Recommendations made for 79 of 94 participants in intervention group (84.0%). No recommendations given to 15 participants because no need for additional advice on top of usual care could be identified. Of 338 recommendations for 79 participants, adherence could not be determined for nine recommendations, leaving 329 recommendations for study (97.3%). The occupational therapist made nine recommendations with unknown adherence, suggesting walking aids or adapted footgear. Mean number of recommendations per participant was 4.3+/- 2.1 (range 1-10). Complete adherence: 56.8%, partial adherence 10.6%. Trauma ward team did not comply with 32.5% of recommendations.	NR
Gagnon 2012 [14]	CRS score assigned: 91.2%. Adherence to CAM: 39%. Overall adherence to study protocols: 89.7%. Pharmacological risk alert: 91.2%, Orientation protocol: 84.5%, Family intervention: 84.1%. Most common reasons for noncompliance with study protocols were pharmacological sedation and coma. Main reason for missed family intervention was absence of a relative.	CAM was not used as an outcome measure as per study protocol as it was obtained in only 39% of patients (due to challenges conducting the baseline CAM structured interview in the last days or hours of life). Delays in completion also rendered results invalid.
Martinez 2012 [15]	NR	NR
Van Rompaey 2012 [16]	"No accidental or intentional removal of the earplugs was reported."	NR
Black 2011 [17]	NR	During pilot phase, there was a change to the study protocol allowing the study information and booklet to be given to families on admission rather than wait until the researcher was present, following feedback from two families.
Bo 2009 [18]	NR	NR
Vidan 2009 [19]	Overall rate of adherence (percentage of actions per days performed in each of the seven targeted intervention domains): 75.7% of patient-days per intervention actions. Highest was mobilization: 91%, lowest was sleep preservation: 50%.	NR

Caplan & Harper 2007 [20]	NR	NR
Lundström 2007 [21]	27 eligible patients excluded due to failed inclusion routines. More documented assessment of underlying causes of delirium in the intervention ward compared with the control ward (2.28±1.25 vs 0.90±0.90, p <0.001), also more documented treatments for underlying causes of delirium (1.69±1.56 vs 0.56±0.98, p <0.001). Delirious control patients more often given sedatives (41.7% vs 15.4%, p =0.008) and opioid drugs on demand (61.7% vs 30.8%, p =0.004) than intervention participants.	NR
Taguchi 2007 [22]	Bright light therapy started at 3.1+/-1.4 days after surgery and performed over a mean of 2.8+/-0.9 days for 110+/-14 min each day	NR
Lundström 2005 [23]	NR	NR
Wong 2005 [24]	Daily CAM ratings 97.2%. Geriatric registrar recommendation (average six/patient) 89.9%. **Recommendations:** Regulation of bladder and bowel function 24%, Early detection/treatment of major complications 22%, Correction of fluid and electrolyte imbalance 14.4%, Discontinuation of unnecessary medications 13.8%, Provision of adequate oxygen delivery 8.5%, Treatment of severe pain 5.4%, Treatment of agitated delirium 4.3%, Use of appropriate environmental stimuli 3.4%, Adequate nutritional intake 2.4%, Early mobilization and rehabilitation 1.8%	NR
Cole 2002 [25]	97% patients received the intervention (mean of 1.4 days after enrolment) as planned. Consultants had a mean of 1.96 contacts (median 1.0, range 1–6) with each patient in the intervention group and made a mean of 6.02 recommendations (median 1.0, range 1–17) per patient, most frequently for medication changes or investigations. **Recommendations:** Medication changes 73.2%, investigations 69%, other recommendations (e.g., patient supports, mobilization) 20.6%. Study nurse contact with each patient: mean of 11.7 (SD 9.8) (median 8.0, range 1–39), lasting a mean of 35.7 (SD 28.8) minutes (median 30, range 5–240). Mean total time spent with each patient was 418 (SD 282) minutes (median 318, range 90–1315). Four most frequent study nurse activities were assessment and support of patients, and education and support of nursing staff and families. **I vs C comparisons:** Geriatric or geriatric psychiatry consultation 100% v.18%, Study nurse visit 100% v. 0%, Documentation of delirium by attending physicians 41% v. 27%, p = 0.03, Decreases in medication 66.4% v. 57.9%, p = 0.19, Occupational therapy, recreational therapy or social work consultation 64.6% v. 54.4%, p = 0.12, Emotional support by ward nurses 14.3% v. 9.4%, p = 0.70, Orienting cues by ward nurses 23.2% v. 16.7%, p = 0.22, Personal possessions at the bedside 35.4% v. 22.8%, p = 0.04.	NR
Marcantonio 2001 [26]	Initial geriatrics consultation preoperatively 61%, remainder had initial consultation within 24 hours of surgery. 591 recommendations/mean of 9.5 recommendations per patient (range 3–21). Overall adherence rate by orthopedics team: 77%. Data did not describe overall management; therefore, comparable data were not available for the usual-care group. Consultants did not recommend things that the orthopedists or nurses were already doing; only when something was not being done that they felt should be. **Recommended/adhered: Adequate CNS oxygen delivery**: Supplemental oxygen to keep saturation >90%, preferably >95% 29%/ 89%, Treatment to raise systolic blood pressure >2/3 baseline or >90 mmHg 4 6%/100%, Transfusion to keep hematocrit >30% 92%/79%, **Fluid/electrolyte balance:** Treatment to restore serum sodium, potassium, glucose to normal limits (glucose <300 mg/dl, <16.5 mmol/L for diabetics) 37%/96%	NR

	Treat fluid overload or dehydration detected by examination or blood tests 48%/90% **Treatment of severe pain:** Around-the-clock acetaminophen (1 gram four times daily) 40%/32% Early-stage break-through pain: low-dose subcutaneous morphine, avoid meperidine 21%/62%, Late-stage break-through pain: oxycodone as needed 5%/67%, **Elimination of unnecessary medications:** Discontinue/minimize benzodiazepines, anticholinergics, antihistamines 68%/83%, Eliminate drug interactions, adverse effects, modify drugs accordingly 21%/54%, Eliminate medication redundancies 13%63% **Regulation of bowel/bladder function:** Bowel movement by postoperative day 2 and every 48 hours 68%57%, D/c urinary catheter by postoperative day 2, screen for retention or incontinence 71%/89%, Skin care program for patients with established incontinence 3%/100% **Adequate nutritional intake:** Dentures used properly, proper positioning for meals, assist as needed 56%/66%, Supplements: 1 can Ensure,* 3 cans Ensure* for poor oral intake 35%/45%, If unable to take food orally, feed via temporary nasogastric tube 2%/100% **Early mobilization and rehabilitation:** Out of bed on postoperative day 1 and several hours daily 58%/81% Mobilize/ambulate by nursing staff as tolerated, such as to bathroom 29%/72%, Daily physical therapy; occupational therapy if needed 2%/100% **Prevention, early detection, and treatment of major postoperative complications:** Myocardial infarction/ischemia—electrocardiogram, cardiac enzymes if needed 34%/81% Supraventricular arrhythmias/atrial fibrillation—appropriate rate control, electrolyte adjustments, anticoagulation 5%/3 100%, Pneumonia/chronic obstructive pulmonary disease - screening, treatment, including chest therapy 44%/67%, Pulmonary embolus -appropriate anticoagulation 50%/100%, Screening for and treatment of urinary tract infection 52%/63% **Appropriate environmental stimuli:** Appropriate use of glasses and hearing aids 5%/67%, Provision of clock and calendar 0%, If available, use of radio, tape recorder, and soft lighting 0% **Treatment of agitated delirium:** Appropriate diagnostic workup/management 2%/100%, For agitation, calm reassurance, family presence, and/or sitter 3%/100%, For agitation, if absolutely necessary, low-dose haloperidol 0.25–0.5 mg every 4 hours as needed; if contraindicated, use lorazepam at same dose 19%/83%.	
Milisen 2001 [27]	NR	NR
Inouye 1999 [28]	Overall rate of adherence (complete and partial adherence, based on patient days) to all intervention protocols: 87%. Orientation protocol 96%, vision protocol 92%, hearing protocol 92%, therapeutic activities 86%, early mobilization 84%, volume repletion 81%, non-pharmacological sleep protocol 71%. Most common reasons for non-adherence included refusal by the patient, lack of availability of patient because of procedures elsewhere in the hospital, medical contraindications, and lack of availability of intervention staff members.	NR
Cole 1994 [29]	Initial recommendations made for all 39 patients in the intervention group who were assessed on admission, with 25 follow-up recommendations. **Initial recommendations:** Investigations (n=4), drug prescriptions (n=3), other (n=7) or a combination (n=25). **Follow-up recommendations:** investigations (n=1), drug prescriptions (n=1), other (n=3) or a combination (n=20). Number of nurse follow-up notes 0-8 (mean 3); 97% of eligible notes completed. **Rates of full compliance with initial recommendations ranged from:** Other 96% - investigations 77%. **Rates for follow-up recommendations ranged from**: Other 91% - investigations 50%.	NR

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Author, year	Adverse events
Moon 2015 [1]	Mortality – see Table 3
Bakker 2014 [2]	≥1 Complication 45% v. 40%
Bryczkowski 2014 [3]	Restraint-free days/30 mean 27 (95% CI 26, 29) v. mean 28 (95% CI 27, 29)
Chong 2014 [4]	[Before v. Intervention v. Control] Physical restraint use: 44.7% v. 0 v. 23.1*, Chemical restraint use: 72.3% v. 40.3% v. 33.3%, Falls: 2.1% v. 1.3% v. 2.6%, Urinary catheter use: 31.9% v. 29.1% v. 25.6, Pressure ulcer rate: 9.1% v. 4.1% v. 1.3%*, Nosocomial infection: 23.4% v. 10.7% v. 7.7%*
Patel 2014 [5]	NR
Gruber-Baldini 2013 [6]	Infections 4.6% vs 4.2%, PE 3.0% vs 0, CHF 1.5% vs 2.8%, Hemorrhaging (>100cc) 9.1% vs 5.6%
Hempenius 2013 [7]	Postoperative complications: Pulmonary 24.4% vs 20.3%, Neurological 6.3% vs 6.0%, Cardiovascular 31.5% vs 27.8%, Thromboembolic 0.8% vs 0, Bleeding 8.7% vs 4.5%, Wound infection 10.2% vs 9.0%, Wound dehiscence 3.1% vs 3.0%, UTI 6.3% vs 5.3%, Anastomotic leakage 3.9% vsn1.5%, Pressure ulcer 3.9% vs 5.3%, RF 3.9% vs 1.5%, Electrolyte disturbance 11.8% vs 9.0%, Fall 3.1% vs 1.5%, Urinary retention 11.8% vs 9.0%, Ileus/gastroparesis 7.1% vs 10.5%
Holt 2013 [8]	Mortality – see Table 3
Jeffs 2013 [9]	"No adverse events were reported."
Kamdar 2013 [10]	Mortality – see Table 3
Zaubler 2013 [11]	NR
Andro, 2012 [12]	NR
Deschodt 2012 [13]	Mortality – see Table 3
Gagnon 2012 [14]	NR
Martinez 2012 [15]	Falls 0 v. 2.8%
Van Rompaey 2012 [16]	NR
Black 2011 [17]	NR
Bo 2009 [18]	NR
Vidan 2009 [19]	Results reported graphically, no exact figures. Physical restraints approximately 2% v. 10%*, Falls approximately 2% v. 1%
Caplan & Harper 2007 [20]	Falls 6.3% vs 19%, Increased unplanned readmissions at 1 month 31.3% vs 19%
Lundström 2007 [21]	Anemia 86.3% vs 82.3%, Constipation 37.3% vs 48.5%, Decubitus ulcers 8.8% vs 22.1%*, Depression 49.5% vs 54.6%, Diarrhea 21.6% vs 27.1%, HF 5.9% vs 11.6%, Pneumonia 4.9% vs 3.1%, UTI 31.4% vs 51.0%* Other infections, 17.8% vs 17.7%, Sleeping problems 27.5% vs 45.4%*, MI 2% vs 4.1%, Nutritional complications 24.5% v. 38.1%, PE 2% vs 0, Stroke 0 vs 1%, Stomach ulcers 3%) vs 4.1%, Urinary retention 15.7% vs 18.6%, Falls 11.8% vs 26.8%*
Taguchi 2007 [22]	NR
Lundström 2005 [23]	Mortality – see Table 3
Wong 2005 [24]	NR
Cole 2002 [25]	Mortality – see Table 3
Marcantonio 2001 [26]	NR
Milisen 2001 [27]	Mortality – see Table 3
Inouye 1999 [28]	"No adverse effects were associated with the intervention protocols."
Cole 1994 [29]	Restraint use 37% v. 29%

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1 (registration)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

PALLIATIVE MEDICINE AUTHOR SUBMISSION CHECKLIST

Please complete this checklist for all papers submitted. Please indicate, very briefly, how this has been addressed. This checklist is a mandatory upload on submission.

Item	Explanation	How this has been addressed (briefly, a sentence will suffice)
Article title	***WHY: Because we want readers to find your work.*** Have you followed our guidelines on writing a good title that will be found by search engines? (E.g. with methods in the title, use of common words for the issue addressed, no country names, and possibly indicating findings). If your study has an acronym is it included in the title?	Yes
Abstract	***WHY: Because structured abstracts have more detail for readers and search engines.*** Have you followed our guidelines on writing your structured abstract? Please remember we have separate abstract structures for original research, reviews and case reports. There should be **no** abbreviations in the abstract, EXCEPT a study acronym which should be included if you have one. If a trial (or other design formally registered with a database) have you included your registration details?	Yes
Key statements	***WHY: Because readers want to understand your paper quickly.*** Have you included our key statements within the body of your paper (after abstract and before the main text is a good place!) and followed our guidelines for how these are to be written? There are three main headings required, and each may have 1-3 separate **bullet** points. Please use clear, succinct, single sentence separate bullet points rather than complex or multiple sentences.	Yes
Keywords	***WHY: Because MeSH headings mean it is properly indexed.*** Have you given keywords for your study? We ask that these are current **MeSH** headings unless there is no suitable heading for use (please give explanation in cover letter). https://meshb.nlm.nih.gov/search	Yes
International relevance	***WHY: We have readers from around the world who are interested in your work.*** Have you contextualised your work for an international audience and explained how your work contributes to an international knowledge base? Avoid drawing from policy from one context only, think	Yes

	how your work could be relevant more widely. Do define terms clearly e.g. hospice has a different meaning in many countries.	
Publishing guidelines	***WHY: Because clear and robust reporting helps people interpret your work accurately*** Have you submitted a completed checklist for a relevant publishing guideline as a supplementary file? http://www.equator-network.org/ These include CONSORT, PRISMA, COREQ checklists, but others may be more relevant for your type of manuscript. If no published checklist exists please create one as a table from the list of requirements in your chosen guideline. If your study design does not have a relevant publishing guideline please review closest matches and use the most appropriate with an explanation.	Yes - PRISMA
Word count	***WHY: Because readers want to find the core information quickly.*** Does your paper adhere to our word count for your article type? Please insert number of words in the box to the right. Remember that tables, figures, qualitative data extracts and references are not included in the word count.	5550
Figures and tables and/or quotations	***WHY: Because readers want to find the core information quickly.*** Have you adhered to our guidelines on the number of tables and figures for your article type? Data (e.g. quotations) for qualitative studies are not included in the word count, and we prefer that they are integrated into the text (e.g. not in a separate table).	Yes
Study registration	***WHY: Because this means readers understand how you planned your study*** Where appropriate have you included details (including reference number, date of registration and URL) of study registration on a database e.g. trials or review database. If your study has a published protocol, is this referenced within the paper?	Yes
Other study publications?	***WHY: So readers can understand the full context of your study*** If there are other publications from this study are these referenced within the body of the paper? Please do not reference papers in preparation or submitted, but in-press publications are acceptable.	NA
Scales, measures or questionnaires	***WHY: So readers can understand your paper in the context of this information*** If your study primarily reports the development or testing of scales/measures or questionnaires have you included a copy of the instrument as a supplementary file?	NA

Abbreviations	***WHY: Because abbreviations make a paper hard to read, and are easily misunderstood*** Have you removed **all** abbreviations from the text except for extremely well known, standard abbreviations (e.g. SI units), which should be spelt out in full first? We do not allow abbreviations for core concepts such as palliative or end of life care.	Yes
Research ethics and governance approvals for research involving human subjects	***WHY: We will only publish ethically conducted research, approved by relevant bodies*** Have you given full details of ethics/governance/data protection approvals with reference numbers, full name of the committee(s) giving approval and the date of approval? If such approvals are not required have you made it explicit within the paper why they were not required. Are details of consent procedures clear in the paper?	NA
Date(s) of data collection	***WHY: So readers understand the context within which data were collected*** Have you given the dates of data collection for your study within the body of your text? If your data are over 5 years old you will need to articulate clearly why they are still relevant and important to current practice.	Yes
Structured discussion	***WHY: So readers can find key information quickly*** Papers should have a structured discussion, with sub headings, summarising the main findings, addressing strengths and limitations, articulating what this study adds with reference to existing international literature, and presenting the implications for practice.	Yes
Case reports	***WHY: So that participants are protected, and its importance made clear*** If your study is a case report have you followed our clear structure for a case report, including highlighting what research is needed to address the issue raised? Have you made clear what consent was required or given for the publication of the case report? Have you provided evidence of such consent as a supplementary file to the editor?	NA
Acknowledgements and declarations	***WHY: So readers understand the context of the research*** Have you included a funding declaration according to the SAGE format? Are there acknowledgements to be made? Have you stated where data from the study are deposited and how they may be available to others? Have you conflicts of interest to declare?	Yes

Supplementary data and materials	***WHY: So the context is clear, but the main paper succinct for the reader*** Is there any content which could be provided as supplementary data which would appear only in the online version of accepted papers? This could include large tables, full search strategies for reviews, additional data etc.	Yes
References	***WHY: So people can easily find work you have referenced*** Are your references provided in SAGE Vancouver style? You can download this style within Endnote and other referencing software.	Yes
Ownership of work.	Can you assert that you are submitting your original work, that you have the rights in the work, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you.	Yes